



ADVANCES IN HETEROCYCLIC CHEMISTRY

Volume 24

A. R. Katritzky &
A. J. Boulton

Advances in
**Heterocyclic
Chemistry**

Volume 24

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Advances in

HETEROCYCLIC CHEMISTRY

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Preface

This volume makes a major contribution to the process of up-dating earlier volumes that we have initiated. Seven of the nine chapters are devoted to this purpose and from now on we intend to up-date chapters from 10 to 15 years after their appearance, provided that considerable work has been carried out in the area covered.

Five chapters have been up-dated by the authors of the original chapters that appeared in earlier volumes, as follows: Quinazolines, by W. L. F. Armarego (the original chapter appeared in Volume 1), Three-membered Rings with Two Heteroatoms, by E. Schmitz (Volume 2), Physicochemical Aspects of Purines, by J. H. Lister (Volume 6), Reissert Compounds, by F. D. Popp (Volume 9), and Pyridazines, by M. Tišler and B. Stanovnik (Volume 9).

Two other chapters up-date subjects covered in earlier volumes, but by different authors: Selenium–Nitrogen Heterocycles, by I. Lalezari, A. Shafiee, and M. Yalpani, which up-dates the contribution by Bulka in Volume 2 on Selenazole Chemistry, and Pyrrolizidines, by D. J. Robins, which up-dates the contribution by Kochetkov and Likhoshesterov in Volume 5.

Finally, two chapters deal with substantially new topics: Benzo[c]cinolines, by J. W. Barton, and 1, 4-Thiazines, by R. J. Stoodley.

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Quinazolines

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I. Introduction

More than 14 years have elapsed since a chapter on quinazolines¹ was published in "Advances in Heterocyclic Chemistry," and an updating is

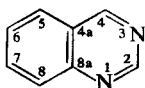
¹ W. L. F. Armarego, *Adv. Heterocycl. Chem.* **1**, 253 (1963).

warranted. In the intervening years, however, a monograph on quinazolines has appeared (1967),² and progress in this field during the periods 1970–1971 and 1972–1973 has been described in two separate reports.^{3,4} The present chapter endeavors to fill the gaps without repeating information already discussed in previous reviews. The interest in quinazolines, as judged by the number of publications, has been partly for their theoretical, physical, and spectroscopic properties, but mostly for the variety of biological activity the derivatives show. Much of this latter work is in the patent literature, and only a few patents can be included here because many of the syntheses and reactions they report are standard in quinazoline chemistry. In this review novel syntheses, properties, and reactions are highlighted, together with modifications of known syntheses and unusual reactions that have been examined in more detail recently.

II. Physical Properties of Quinazolines

A. THEORETICAL STUDIES AND SPECTRA

The *resonance energies* of several nitrogen heterocyclic compounds including quinazoline (**1**) were evaluated from bond energies using calculated heats of formation and bond lengths.⁵ The data implied that there is much bond localization in the heterocycles. The resonance energy for quinazoline



(1)

(127.2 kJ mol⁻¹) is very similar to the isoconjugate hydrocarbon naphthalene (127.7 kJ mol⁻¹), and should be contrasted with quinoline (137.9 kJ mol⁻¹) and pyrimidine (84.5 kJ mol⁻¹).

The *dipole moment* of quinazoline was calculated from variable electro-negativity self-consistent field (VESCF) molecular orbital procedures with

² W. L. F. Armarego, in "Fused Pyrimidines. Part 1—Quinazolines" (D. J. Brown, ed.), Wiley (Interscience), New York, 1967.

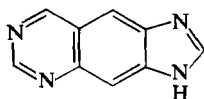
³ W. L. F. Armarego, in "MTP International Review of Science. Organic Chemistry Series One. Heterocyclic Compounds" (K. Schofield, ed.), Vol. 4, pp. 153–156. Butterworth, London, 1973.

⁴ W. L. F. Armarego, in "MTP International Review of Science. Organic Chemistry Series Two. Heterocyclic Compounds" (K. Schofield, ed.), Vol. 4, pp. 160–165. Butterworth, London, 1975.

⁵ M. J. S. Dewar, A. J. Harget, and N. Trinajstić, *J. Am. Chem. Soc.* **91**, 6321 (1969).

BJ (2.55 D) and CJ (2.40 D) integral prescriptions, which gave better values than previous theoretical methods.⁶ The observed dipole moment in benzene was 2.2 D, and the agreement between theory and experiment for other heterocycles that were studied was also within 0.4 D.

Several attempts were made to calculate the *ultraviolet electronic spectra* of quinazoline and other azaheterocycles. Semiempirical Pariser–Parr–Pople (PPP) calculations gave transition energies and bond distances in satisfactory agreement with experimental data.^{7,8} It was also possible to predict the polarizations of the first two transitions in the PPP approximation,⁹ and other data¹⁰ using Mataga's modification¹¹ with resort to limited or no configurational interaction (CI). The ultraviolet spectrum of quinazoline vapor was photographed, and the vibrations of the strong band were analyzed. The lowest $n\text{--}\pi^*$ transition was shown to have its origin at $27,581\text{ cm}^{-1}$ and was made up of two strong and prominent progressions at 515 and 784 cm^{-1} .¹² Molecular orbital calculations by a modified INDO method gave a value of ν_{max} at $30,648\text{ cm}^{-1}$ for the $n\text{--}\pi^*$ transition. Other bands reported for quinazoline in water (pH 7) at 32,700, 36,800, and $45,000\text{ cm}^{-1}$ were correlated with the $\pi\text{--}\pi^*$ transitions calculated at 33,500, 38,100, and two bands at 45,600 and $47,100\text{ cm}^{-1}$, respectively. The oscillator strengths are not available for quinazoline but the calculated values are in good agreement with the reported ϵ_{max} and the band shapes.¹³ Further studies of the electronic spectra of quinazolines revealed in the spectra diffuseness that was attributed to rapid electronic relaxation (radiationless transitions). The spectra of the vapor, and in pure and mixed crystals, were studied.^{14,15} The spectra revealed a sharp first system of bands, which rises in a simple pattern of progressions from $27,587\text{ cm}^{-1}$. The second system (first $\pi^* \leftarrow \pi$) is diffuse.¹⁴



(2)

⁶ R. D. Brown and B. A. W. Collier, *Theor. Chim. Acta* **7**, 259 (1967).

⁷ B. Tinland, *Theor. Chim. Acta* **8**, 361 (1967).

⁸ M. Sundbom, *Acta Chem. Scand.* **25**, 487 (1971).

⁹ J. Koutecký, *J. Chem. Phys.* **47**, 1501 (1967).

¹⁰ W. R. Carper and J. Stengl, *Mol. Phys.* **16**, 627 (1969).

¹¹ K. Nishimoto and N. Mataga, *Z. Phys. Chem. (Frankfurt am Main)* **12**, 335 (1957).

¹² Y. Hasegawa, Y. Amako, and H. Azumi, *Bull. Chem. Soc. Jpn.* **41**, 2608 (1968).

¹³ J. E. Ridley and M. C. Zerner, *J. Mol. Spectrosc.* **50**, 457 (1974).

¹⁴ J. P. Byrne and I. G. Ross, *Aust. J. Chem.* **24**, 1107 (1971).

¹⁵ A. D. Jordon and I. G. Ross, *J. Mol. Spectrosc.* **46**, 316 (1973).

Leonard and co-workers^{16,17} have extended the adenine molecule by synthesizing the benz-analog in which the benzene ring is placed between the imidazole and the pyrimidine rings, e.g., *lin*-benzoadenine (2). They also made the angular isomers *prox*- and *dist*-benzadenine. These imidazoquinazolines have much more elaborate ultraviolet spectra (more absorption at longer wavelengths) than adenine or 4-aminoquinazoline, and the spectra undergo large changes with varying pH of the medium. *lin*-Benzoguanine, in which the heterocyclic rings are separated by ca. 2.4 Å has, in addition, fluorescent properties.¹⁸ These properties should be useful for tracing these molecules in biological systems.

The *fluorescence* and *phosphorescence* of quinazoline, 6-chloro-4-phenyl- and 6-chloro-1-methyl-4-phenylquinazolin-2(1*H*)-one were recorded in ethanol containing 1% of concentrated sulfuric acid. The *luminescence* of these compounds on thin-layer chromatography (TLC) plates saturated with ethanol was reported.¹⁹ 4-Morpholino- and 4-piperidino-6-methoxy-2-phenylquinazoline also have luminescent properties, and the ultraviolet fluorescence in the crystals and in hexane or benzene solution was discussed.²⁰ The time and wavelength resolved emission from quinazoline vapor at low pressures was studied with a pulsed frequency double-dye laser and were compared with those of quinoxaline and cinnoline.²¹

The *photoelectron spectrum* of quinazoline was measured, and had bands between 8 and 16 eV.^{22,23} Band assignments were proposed by comparison with the spectra of other related nitrogen heterocycles,^{22,23} and by estimations of the ionization potentials using molecular orbital calculations.^{24,25} The high-resolution He 584 Å photoelectron spectra of quinazoline, 2- and 4-fluoro-, 2,4-difluoro, and hexafluoroquinazoline were measured. Fluorine substitution gave spectra from which the analysis of the bands in the parent compound was more definite.^{23,26} Unexpected shifts of N lone-pairs were interpreted in terms of through-space and through-bond interactions, and

¹⁶ N. J. Leonard, A. G. Morrice, and M. A. Sprecker, *J. Org. Chem.* **40**, 356 (1975).

¹⁷ A. G. Morrice, M. A. Sprecker, and N. J. Leonard, *J. Org. Chem.* **40**, 363 (1975).

¹⁸ G. E. Keyser and N. J. Leonard, *J. Org. Chem.* **41**, 3529 (1976).

¹⁹ J. A. F. de Silva, N. Strojny, and K. Stika, *Anal. Chem.* **48**, 144 (1976).

²⁰ B. V. Golomolzin, L. D. Shcherak, and I. Ya. Postovskii, *Khim. Geterotsikl. Soedin.*, 1131 (1969) [CA **72**, 121480 (1970)].

²¹ R. J. McDonald and L. E. Brus, *J. Chem. Phys.* **61**, 3895 (1974).

²² F. Brogli, E. Heilbronner, and T. Kobayashi, *Helv. Chim. Acta* **55**, 274 (1972).

²³ D. M. W. van den Ham and D. van der Meer, *J. Electron Spectrosc. Relat. Phenom.* **2**, 247 (1973).

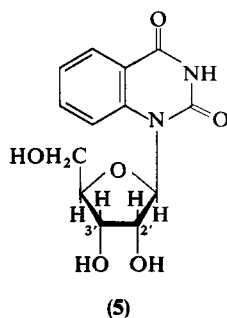
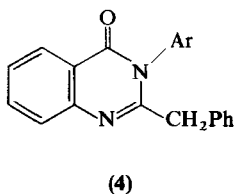
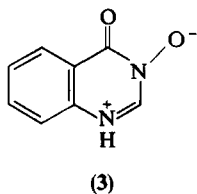
²⁴ M. J. S. Dewar and S. D. Worley, *J. Chem. Phys.* **51**, 263 (1969).

²⁵ J. Spanget-Larsen, *J. Electron Spectrosc. Relat. Phenom.* **3**, 369 (1974).

²⁶ D. M. W. van den Ham, M. Beerlage, D. van der Meer, and D. Feil, *J. Electron Spectrosc. Relat. Phenom.* **7**, 33 (1975).

fluorine substitution gave experimental evidence about the symmetry of the "lone-pair" molecular orbitals. The ionization potentials have been correlated with the first pK_a of heteroaromatic compounds, and the value for quinazoline (1.5) was in satisfactory agreement with the experimental value.^{22,27}

The *infrared spectrum* of quinazoline and other diazanaphthalenes were measured, and the vibrational fundamentals were assigned from Raman polarization data. The *Raman spectrum* of quinazoline in aqueous solution has fourteen bands that appear to be polarized. All the band frequencies, except for those at 1330 and 1334 cm^{-1} , were consistent with the frequencies assigned as fundamentals in the spectrum of naphthalene.²⁸ The infrared spectra of several quinazolin-4(3*H*)-ones and their 3-acetyl, 3-acetoxy, and 3-hydroxy derivatives were examined at wave numbers lower than 3000 cm^{-1} . Bands due to NH stretching vibrations provided evidence for cyclic dimeric association between molecules. The zwitterionic structure (3) was proposed for 3-hydroxyquinazolin-4-one.²⁹



A comparison was made between excess charges on the atoms in quinazoline deduced from proton chemical shift data and those obtained by theoretical calculations using the BJ. VESCF method. The v.m.s. error was of the order of 0.011 (charge difference), and similar errors were obtained for other nitrogen heterocycles that were studied.³⁰ The *proton magnetic resonance* (PMR) spectra of eight 3-aryl-2-benzylquinazolin-4-ones (4) in nitrobenzene or bromoform contained an AB quartet of signals for the benzylic protons on C-2 at $\delta \sim 3.8$ ppm. When the aryl group had no substituents in the ortho positions (e.g., 3-*m*-bromophenyl), the quartet collapsed on heating, indicating restricted rotation about the N_3 —Ar bond with a free energy

²⁷ M. Ciureanu and V. E. Sahini, *Rev. Roum. Chim.* **20**, 1037 (1975) [*CA* **84**, 4270 (1976)].

²⁸ R. W. Mitchell, R. W. Glass, and J. A. Merritt, *J. Mol. Spectrosc.* **36**, 310 (1970).

²⁹ P. Sohar and I. Kosa, *Acta Chim. Acad. Sci. Hung.* **57**, 411 (1968) [*CA* **70**, 4024 (1969)].

³⁰ P. J. Black, R. D. Brown, and M. L. Heffernan, *Aust. J. Chem.* **20**, 1305 (1967).

barrier (ΔG^\ddagger) of ca 79.5 kJ mol^{-1} . This barrier increased to 99 kJ mol^{-1} when a halogen atom was present in the *o*-position of the 3-aryl ring.³¹ The PMR chemical shifts of fourteen quinazoline-2,4(1*H*, 3*H*)-diones substituted at N-1 and/or N-2, and/or C-6 were also reported, and the signals were assigned.³² The protons on C-2' and C-3' of the furanose ring of the quinazoline nucleoside (**5**) were deshielded, presumably by the benzene ring, indicating that the syn conformation was predominant.³³ The shift reagent $\text{Eu}(\text{fod})_3$ was shown to complex with substituted quinazolines, and from the slopes of the curves (δ vs. $\text{Eu}(\text{fod})_3$ concentration) steric effects could be demonstrated.³⁴

The ^{13}C magnetic resonance spectrum of quinazoline was measured in benzene. The chemical shift values were rationalized by a theoretical treatment and were compared with those of other heterocycles. The assignment for the carbon atoms relative to benzene were C-2 (-31.99 ppm), C-4 (-27.20), C-4a ($+3.29$), C-5 ($+1.10$), C-6 ($+0.57$), C-7 (-5.63), C-8 (-0.06), and C-8a (-21.63) (see also Table I).³⁵

The optical nuclear polarization of quinazoline in hexadeuterobenzene was obtained by irradiation with an SP 1000 Philips lamp. The protons at C-2 and C-4 exhibited very strong and strong absorption polarization, respectively. The polarization of the hydrogens α to the heteroatoms were governed by the distance between the nitrogen atoms. For comparison, H-2 and H-4 in quinoxaline showed absorption polarization, but H-1 and H-4 in phthalazine and H-3 and H-4 in cinnoline exhibited no polarization.³⁶

Fragmentation of quinazolines upon electron bombardment gave mass spectra which showed that the heterocyclic ring breaks up before the benzene ring. The spectra of many quinazolines with a variety of substituents other than oxo were examined. Substituents at C-4 were lost in preference to substituents at C-2, and quinazolines with substituents at C-5 and C-8 gave fragments which were different from the other isomers because of *peri* effects.³⁷ Quinazoline 3-oxides lose the oxygen atom first and then fragment

³¹ L. D. Colebrook and H. G. Giles, *Can. J. Chem.* **53**, 3431 (1975).

³² M. Khalife el Saleh, G. Pastor, C. Montginoul, E. Torreilles, L. Giral, and A. Texier, *Bull. Soc. Chim. Fr.*, 1667 (1974).

³³ M. P. Schweizer, E. B. Banta, J. T. Witkowski, and R. K. Robins, *J. Am. Chem. Soc.* **95**, 3770 (1973).

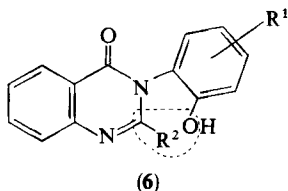
³⁴ J. Dusemund and K. Roth, *Z. Naturforsch., Teil B* **31**, 509 (1976).

³⁵ R. J. Pugmire, D. M. Grant, M. J. Robins, and R. K. Robins, *J. Am. Chem. Soc.* **91**, 6381 (1969).

³⁶ G. Vermeersch, N. Febvay-Garot, S. Caplain, and A. Lablache-Combier, *Tetrahedron Lett.*, 2991 (1975).

³⁷ T. J. Batterham, A. C. K. Triffett, and J. A. Wunderlich, *J. Chem. Soc. B*, 892 (1967).

like the respective quinazolines.³⁸ Quinazolinones behaved in a different way, although here again the heterocyclic ring fragmented before the benzene



ring. A novel fragmentation was observed in the mass spectra of the 3-*o*-hydroxyphenylquinazolin-4-ones (**6**: $R^2 = H$; Me; and Et) which gave carbon monoxide, ketene, and ethyl ketene, respectively, together with 2-aryldiazolin-3(1*H*)-one. The fragment encircled in **6** was extruded only in the *o*-hydroxy compounds; the *o*-methoxy derivatives gave patterns similar to *o*-unsubstituted 3-arylquinazolin-4-ones.³⁹ The intense ion at $m/e = 32$ corresponding to the fragment $NHOH^{+}$ was obtained from 3-hydroxyquinazoline-2,4-dione on electron impact, indicating that N-3 was extruded. The major fragmentation in the 3-*O*-methyl and 1-methyl derivatives, however, was cleavage of the N_3-O bond; and in the 3-*O*-benzenesulfonyl derivative, cleavage of the $S-O$ bond predominated and gave the $PhSO_2^{+}$ ion.⁴⁰ In general, 4-imino-3-methyl-3,4-dihydropyrimidines and their Dimroth rearrangement products 4-methylaminopyrimidines gave essentially similar fragmentation patterns. On the other hand, 4-imino-3-methyl-3,4-dihydroquinazoline (and its 2-methyl derivative) and 4-methylaminoquinazoline (and its 2-methyl derivative) had different mass spectra. This demonstrated that rearrangement did not take place readily upon electron impact and supported studies in solution showing that the Dimroth rearrangement was slow in the quinazoline series.⁴¹

The *X-ray data* for quinazoline at room temperature were analyzed. The two quinazoline molecules in the asymmetric unit were identical in shape within experimental error. The two molecules were oriented 180° from each other around the $[211]$ direct axis. There was, however, a small but significant deviation ($\sim 0.01 \text{ \AA}$) from planarity within the molecule. The most interesting feature was that the C_4-N_3 and the N_1-C_2 distances were identical (1.307 \AA).⁴²

³⁸ D. J. Brown and B. T. England, *Isr. J. Chem.* **6**, 569 (1968).

³⁹ C. Bogentoft, U. Bondesson, Ö. Ericsson, and B. Danielsson, *Acta Chem. Scand., Ser., B* **28**, 479 (1974).

⁴⁰ K.-Y. Tserng, C. L. Bell, and L. Bauer, *J. Heterocycl. Chem.* **12**, 79 (1975).

⁴¹ D. J. Brown and K. Ienaga, *Heterocycles*, **3**, 283 (1975).

⁴² C. Huiszoon, *Acta Crystallogr., Sect. B* **32**, 998 (1976).

B. IONIZATION AND COVALENT HYDRATION

The acidity of the hydrogen atoms at C-2 and C-4, as measured by hydrogen–deuterium exchange data, could not be correlated with Hückel MO, Pariser–Parr–Pople (PPP), or variable β,γ -PPP localization energies calculations. The deficiency of β -electron methods was probably because of the field effects of the heteroatoms and their lone pairs of electrons.⁴³

Molecular orbital calculations which gave parameters that correlated well with aza analogs of 8-hydroxyquinazoline were applied to quinazoline. By taking covalent hydration into consideration, it was shown that π -electron energies and electron densities at position 1 gave good correlations with the pK_{anhyd} (1.5) for quinazoline and the pK_a values of other heterocycles.⁴⁴ Previously, good correlations were obtained when the pK (unknowingly) of quinazoline (anhydrous) was taken as 3.5 (i.e., $pK_{\text{equil.}}$) instead of ~ 1.5 . Further studies suggested that the $pK_{\text{equil.}}$ value could be explained in terms of a stepwise process requiring two successive protonations of quinazoline followed by hydroxylation at C-4 (however, see below).⁴⁵ Like other nitrogen heterocycles, quinazoline forms a complex with iodine in chloroform, which has an absorption maximum at 430 nm. A good linear correlation between the pK_a values of heterocyclic bases and the $\log K$ values for their iodine complexes was demonstrated. The pK_a for anhydrous quinazoline derived from the relation was 1.56,⁴⁶ and is in satisfactory agreement with the most accurate pK_{anhyd} value (1.95 at 20°C) measured to date.⁴⁷ It is ironical that in a recent theoretical study, using CNDO/2 wave functions and perturbation theory, a correlation was found between the pK_a value of 3.43 and quantum mechanical quantities.⁴⁸ The pK_{equil} value of 3.51 for quinazoline is an equilibrium value involving the true pK_{anhyd} and the ratio of hydrated and anhydrous species K (Eq. 1).⁴⁹

$$pK_{\text{equil}} = pK_{\text{anhyd}} + \log(1 + K) \quad (1)$$

In an investigation of the protonation of weak bases and second protonation of diacidic bases, Katritzky and co-workers⁵⁰ obtained a value of -4.51 for the H_0 value of half-protonation of the quinazoline cation. The value is

⁴³ C. Weiss, F. Höppner, S. Becker, and W. Blaschke, *Tetrahedron* **29**, 3071 (1973).

⁴⁴ A. R. Lepley, M. R. Chakrabarty, and E. S. Hanrahan, *Tetrahedron Lett.*, 6057 (1966).

⁴⁵ A. R. Lepley, M. R. Chakrabarty, and E. S. Hanrahan, *J. Chem. Soc. A*, 1626 (1967).

⁴⁶ I. Ilmet and M. Krasij, *J. Phys. Chem.* **70**, 3755 (1966).

⁴⁷ J. W. Bunting and D. D. Perrin, *J. Chem. Soc. B*, 436 (1966).

⁴⁸ P. van de Weijer, D. van der Meer, and J. L. Koster, *Theor. Chim. Acta* **38**, 223 (1975).

⁴⁹ D. D. Perrin, *Adv. Heterocycl. Chem.* **4**, 43 (1965).

⁵⁰ P. J. Brignell, C. D. Johnson, A. R. Katritzky, N. Shakir, H. O. Tarhan, and G. Walker, *J. Chem. Soc. B*, 1233 (1967).

similar to the second pK_a (-4.40) measured previously,⁵¹ but they observed that quinazoline cation did not behave as a Hammett base because no single acidity function represented the diprotonation equilibria.

The qualitative⁵² and quantitative⁴⁹ aspects of covalent hydration of nitrogen heterocycles were reviewed in 1965 and updated by Albert in 1976.⁵³ A few papers that were not reported or discussed in detail in these reviews are included here.

Yet another very important method for diagnosing covalent hydration requires an examination of the ^{13}C NMR spectra of the anhydrous and the hydrated species. The ^{13}C chemical shifts of the anhydrous neutral species of quinazoline and its hydrated cation have been determined and are in Table I. The deshielding of the C-4 resonance is characteristic for the change from an sp^2 to an sp^3 carbon atom upon hydration. Other heterocycles that are known to undergo covalent hydration showed similar changes in spectra.^{54,55}

TABLE I
 ^{13}C NUCLEAR MAGNETIC RESONANCE CHEMICAL
SHIFTS OF QUINAZOLINE (Me_4Si , δ ppm)⁵⁴

	C-2	C-4	C-4a	C-5	C-6	C-7	C-8	C-8a
Anhydrous neutral Species (CDCl_3)	156.1	161.1	126.0	128.1	128.8	135.1	129.3	151.3
Hydrated cation ($2\text{ N-aq. H}_2\text{SO}_4$)	148.1	72.4	121.4	118.3	129.2	129.2	131.7	130.4

The kinetics of hydration and dehydration for quinazoline and 2-methylquinazoline were studied in great detail by Bunting and Perrin,⁵⁶ and the pH-rate profiles between pH 0.5 and 12.0 were determined. The profiles for quinazoline are illustrated in Fig. 1. The rate of hydration was given by the expression in Eq. (2).

$$k_h = b(a_H +) + c + d/a(\text{H}^+) \quad (2)$$

⁵¹ A. Albert, W. L. F. Armarego, and E. Spinner, *J. Chem. Soc.*, 2689 (1961).

⁵² A. Albert and W. L. F. Armarego, *Adv. Heterocycl. Chem.* **4**, 1 (1965).

⁵³ A. Albert, *Adv. Heterocycl. Chem.* **20**, 117 (1976).

⁵⁴ U. Ewers, H. Günther, and L. Jaenicke, *Angew. Chem., Int. Ed. Engl.* **14**, 354 (1975).

⁵⁵ U. Ewers, A. Gronenborn, H. Günther, and L. Jaenicke, in "Chemistry and Biology of Pteridines" (W. Pfeleiderer, ed.), p. 687, de Gruyter, Berlin, 1975.

⁵⁶ J. W. Bunting and D. D. Perrin, *J. Chem. Soc. B*, 950 (1967).

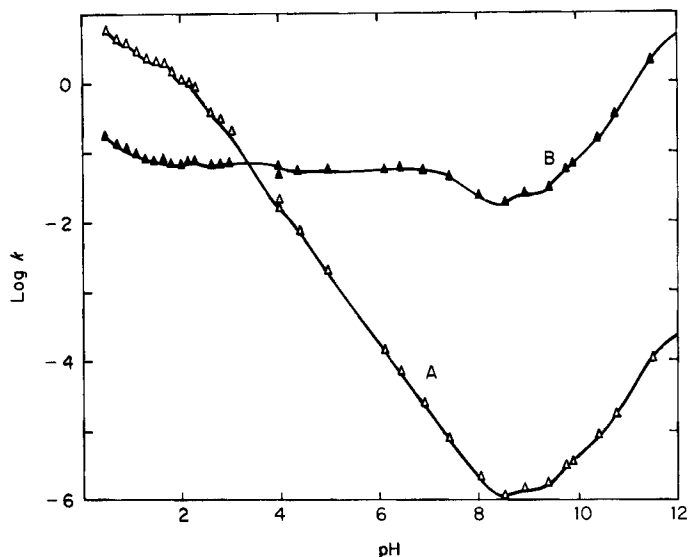
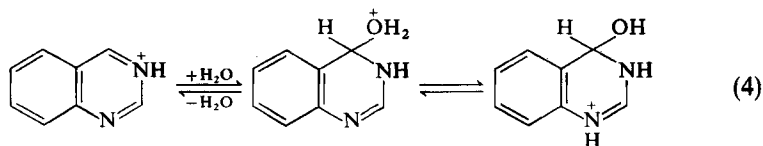


FIG. 1. pH-Rate profiles for the reversible hydration of quinazoline at 20°C: (A) $\log k_h$ and (B) $\log k_a$. Kindly computed by Professor D. D. Perrin.

At lower pH values, another term, $a_1(a_H+)^2$, had to be added to the equation and gave a relationship similar to the expression for the rate of dehydration [Eq. (3)]. The values b , c , d , a_1 , b_1 and c_1 , and d_1 are constants for the particular

$$k_d = a_1(a_H+)^2 + b_1(a_H+) + c_1 + d_1/(a_H+) \quad (3)$$

quinazoline. The first-order rate constants for hydration and dehydration (as calculated from the observed first-order rate constants determined by rapid reaction techniques) of 17 quinazolines over a narrow pH range were determined. These authors suggested the mechanism in Eq. (4) for the hydration of quinazoline when it was protonated on N-3. A similar equation can be written for quinazoline when it is protonated on N-1. The ratio of hydrated to anhydrous neutral species of 28 quinazolines were calculated



from the pK_{equil} values and the pK_a for the hydrated species (determined by rapid reaction techniques); they were all in the region $0.02-79.4 \times 10^{-4}$.⁵⁷ The relative ratios of these compounds were of the same order as those observed for the relative ratios in the respective cations (which are considerably more hydrated),^{47,58} and this suggests, to a first approximation, that the factors influencing hydration in these two species are similar. A rough estimate of the Arrhenius parameters for the hydration and dehydration of quinazoline monocation was made from the rate studies. At 20°C these values were ΔE_a 38.9 ± 2 KJ mol⁻¹ and ΔS^\ddagger -113 ± 8.4 J mol⁻¹ deg⁻¹ for hydration, and ΔE_a 64 ± 2 KJ mol⁻¹ and ΔS^\ddagger -58.6 ± 8.4 J mol⁻¹ deg⁻¹ for dehydration.⁵⁶

The equilibria of addition of the nucleophiles H₂O, HSO₃⁻, NH₂OH, NH₂CONH₂, HSCH₂CH₂OH, and H₂S to quinazoline were examined, and a linear free-energy relationship was noted between log K_{equil} and the γ values of the nucleophile.⁵⁹ The latter values are parameters that give a measure of the ability of the nucleophile to add to aldehydes or ketones.

The covalent addition of water to C=N in an N—C=N system to form a stable hydrate is rare in heterocyclic chemistry. Two examples are known in the quinazoline series, and these are 2-methyl- and 2-phenyltetrazolo[1,5-*c*]quinazoline. In these compounds water addition across the 3,4 double bond is not possible because of ring fusion. When these were treated with hydroxides, the hydrates (7: R = Me and Ph) were isolated and characterized.^{60,61} Undoubtedly such hydrates must be involved as intermediates in the syntheses or hydrolytic degradation of quinazolines in which the C-2, N-3 bond is made or broken. Indirect evidence that a 1,2-covalent hydrate was a necessary intermediate in the bromination of quinazolin-4-one came from judicious kinetic studies. The kinetic order, acidity dependence or rates, inverse dependence of rates on bromide ion, and the relative reactivities of quinazolin-4(3*H*)-one, 3-methylquinazolin-4-one and 1,3-dimethyl-4-oxoquinazolinium perchlorate were consistent with a mechanism in which the rate-determining step was attack of molecular bromine on the 1,2-covalent hydrate, i.e., 8 → 9.⁶²

Quinazoline-5,8-quinones (10) do not undergo reversible water addition in acidic, neutral, or basic aqueous solutions.⁶³

⁵⁷ W. L. F. Armarego and J. I. C. Smith, *J. Chem. Soc. B*, 449 (1967).

⁵⁸ W. L. F. Armarego, *J. Chem. Soc.*, 561 (1962).

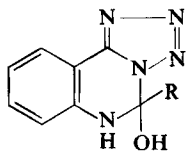
⁵⁹ M. J. Cho and I. H. Pitman, *J. Am. Chem. Soc.* **96**, 1843 (1974).

⁶⁰ I. Ya. Postovskii and N. N. Vereshchagina, *Khim. Geterotsikl. Soedin.*, 944 (1967).

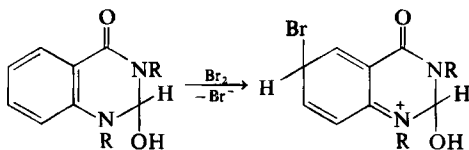
⁶¹ I. Ya. Postovskii and B. V. Golomolzin, *Khim. Geterotsikl. Soedin.*, 100 (1970).

⁶² O. S. Tee and G. V. Patil, *J. Org. Chem.* **41**, 838 (1976).

⁶³ L. I. Kosheleva, Yu. S. Tsizin, and N. B. Karpova, *Khim. Geterotsikl. Soedin.*, 1559 (1974).

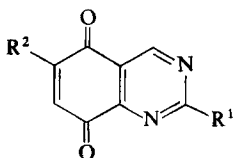


(7)



(8)

(9)



(10)

C. POLAROGRAPHY

The review on the electrolysis of *N*-heterocyclic compounds by Lund in 1970 included a discussion on the polarographic behavior of quinazoline.⁶⁴ The reduction of quinazoline was complicated by covalent hydration in acidic solution, because the hydrated species were not easily reduced.⁶⁵ The anhydrous species in alkaline medium were reduced stepwise to dihydro and then to tetrahydroquinazoline, and the dihydro radical intermediate was capable of dimerization. The protonation rates of *N*-heterocycles in aqueous solution could be determined by polarographic techniques. The rates for quinazoline, and pyrimidine, however, were too fast for measurement which was consistent with predictions from quantum-chemical calculations.⁶⁶

The polarography and cyclic voltammetry of quinazoline were reported, and the reversible half-wave potential was compared with those of other *N*-heteroaromatic compounds.^{67,68} The observed energy differences be-

⁶⁴ H. Lund, *Adv. Heterocycl. Chem.* **12**, 213 (1970).

⁶⁵ H. Lund, *Acta Chem. Scand.* **18**, 1984 (1964).

⁶⁶ D. van der Meer, *Rec. Trav. Chim. Pays-Bas* **89**, 51 (1970).

⁶⁷ S. Millefiori, *J. Heterocycl. Chem.* **7**, 145 (1970).

⁶⁸ K. B. Wiberg and T. P. Lewis, *J. Am. Chem. Soc.* **92**, 7154 (1970).

tween benzazines and their radical anions derived from polarographic data were in good agreement with results from CNDO and self-consistent field π -electron calculations.⁶⁸

The half-wave potentials ($E_{1/2}$) for 4-unsubstituted-, 4-methyl-, 4-phenyl-, 4,1'-pyrrolidinyl-, and 4,4'-pyridyl-2-chloroquinazolines and for 2-unsubstituted-, 2-methyl-, 2-phenyl-, 2,1'-pyrrolidinyl-, and 2,4'-pyridyl-4-chloroquinazolines were measured in dimethylformamide. The values for the latter series gave a satisfactory correlation with the acidic pK_a values of 2-unsubstituted-, 2-methyl-, 2-phenyl-, 2,1'-pyrrolidinyl-, and 2,4'-pyridyl-quinazolin-4(3*H*)-ones measured spectrophotometrically in aqueous solution.⁶⁹

III. Synthesis of Quinazolines and Quinazolinones

A considerable number of quinazolines and quinazolinones are still being prepared by conventional and well known syntheses,^{1,2} but only new and unusual modifications of known synthesis are described in this section. The section is divided into four parts. The first is on the synthesis of quinazolines in which the pyrimidine ring retains its complete aromatic character (i.e., three conjugated double bonds), and the other three parts are on the synthesis of quinazolines with oxygen, and/or sulfur atoms at the 2-, 4-, and 2,4-positions.

A. QUINAZOLINES

The oxygen atom in the aromatic pyrylium salts is known to be readily exchanged (e.g., with ammonia) to provide the respective nitrogen heterocycle.⁷⁰ This substitution in the nucleus is also successful for the quinazoline series and a few 2-substituted-4-phenylquinazolines were prepared by treating 2-substituted-4-phenyl-3,1-benzoxazin-3-ium perchlorates (**11**) with ammonia.⁷¹

Irradiation of aqueous solutions of (*S*)-tryptophan at pH 6–9 containing a photosensitizer (e.g., eosin) caused destruction of the amino acid and formation of *N'*-formylkynurenine as the major product. Similar irradiation in dilute ammonia at pH 8–9 gave an optically active compound in 13% yield, which was shown to be 4-(2'-amino-2'-carboxyethyl)quinazoline (**12**).

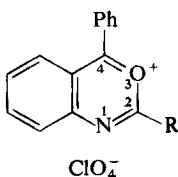
⁶⁹ S. L. Mertsalov, L. G. Egorova, and I. Ya. Postovskii, *Khim. Geterotsikl. Soedin.*, 687 (1970).

⁷⁰ A. T. Balaban, W. Schroth, and G. Fischer, *Adv. Heterocycl. Chem.* **10**, 241 (1969).

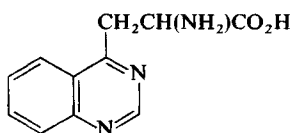
⁷¹ V. I. Dulenko, N. N. Alekseev, and V. M. Golyak, *Khim. Geterotsikl. Soedin.*, 1286 (1976).

Racemic tryptophan similarly gave *d,l*-**12**, the methyl ester and 2-methyl derivatives gave the corresponding quinazolines, but the *N*-acetyl derivative failed to yield a quinazoline and gave *N*-acetyl-*N'*-formylkynurenine. Clearly the pyrrole ring was cleaved, and then reaction with ammonia followed by ring closure, gave the quinazoline.⁷² This is probably how the metabolism of tryptophan takes place in the "quinazoline pathway" in *Pseudomonas*⁷³ (see Section VIII).

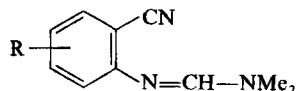
A study of all the stages in the synthesis of 4-aminoquinazolines from isatoic anhydride, via anthranilamide and *o*-aminobenzonitrile, made possible the preparation of these compounds by a one-pot synthesis. The anhydride was treated with ammonia in dimethylformamide, nitrogen was then bubbled through the solution to remove excess of ammonia, phosphoryl chloride was added and heated at 40°–60°C for conversion into the nitrile, and finally the respective amine was added to yield the 4-(substituted-amino)-quinazolines in 44–79% yields.⁷⁴



(11)

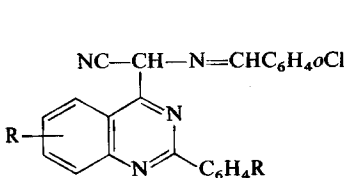


(12)

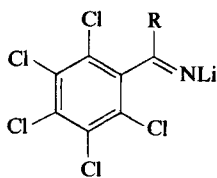


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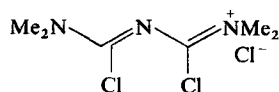
In a novel transformation the β -oximes of isatins gave *o*-*N',N'*-dimethylaminomethyleneaminobenzonitriles (13) with the Vilsmeier reagent ($\text{Me}_2\text{NCHO}-\text{POCl}_3$). The nitriles were cyclized to 4-aminoquinazolines with ammonium acetate in 70–80% yields.⁷⁵



(14)



(15)



(16)

The formation of quinazolines by condensation of nitriles with imidoyl chlorides, or the cations derived from them, in the presence of a Lewis acid

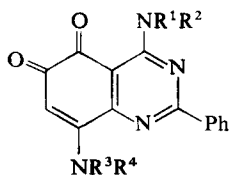
⁷² W. E. Savage, *Aust. J. Chem.* **24**, 1285 (1971).

⁷³ S. Mann, *Arch. Mikrobiol.* **56**, 324 (1967).

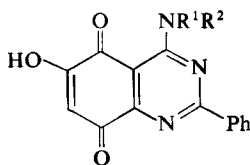
⁷⁴ C. H. Foster and E. U. Elam, *J. Org. Chem.* **41**, 2646 (1976).

⁷⁵ M. N. Deshpande and S. Seshadri, *Indian J. Chem.* **11**, 538 (1973).

had been pioneered by Meerwein and co-workers.⁷⁶ It was hoped that by applying this reaction to *o*-chlorobenzylidene malononitrile a product with a large UV bathochromic shift could be obtained to serve as a method of analysis of the malononitrile. Thus the dinitrile was allowed to react with *N*-arylbenzimidoyl chloride in the presence of aluminum chloride in nitrobenzene or *o*-dichlorobenzene, but only one nitrile function reacted and the products were the corresponding monoquinazolines (14). The quinazoline did not have the required absorption at long wavelengths.⁷⁷ Pentachlorophenyl lithium condensed with aryl and pyridyl nitriles to yield the lithium salt of the imines (15). These gave mixtures of syn and anti imines which were unusually stable, but alkylation of the lithium salts with methyl iodide gave only the *anti-N*-methyl imines. If the condensation was carried out with excess of the nitrile then 2,4-diaryl(or dipyridyl)-5,6,7,8-tetrachloroquinazolines were formed in low to moderate yields. Lewis acids were not necessary for these reactions.⁷⁸ 1,3-Dichlorotrimethinecyanines reacted with amines to form a variety of heterocyclic compounds.^{79,80} The aza analog, 1,3-dichloroazacyanine chloride (16), prepared from *N,N*-dimethylphosgeneiminium chloride and *N,N*-dimethylcyanamide, gave 2,4-dimethylaminoquinazoline in 50% yield.⁸⁰ No doubt other aryl amines with at least one free ortho position will also furnish quinazolines with dimethylamino groups in positions 2 and 4.



(17)



(18)

The copper acetate-catalyzed aerial oxidation of 4-substituted-amino-6-hydroxy-2-phenylquinazolines in methanolic solution containing piperidine or dimethylamine gave the 5,6-quinones (17) in 64–79% yields. Some of these were also formed when 6-acetoxy-4-chloro-2-phenylquinazoline was oxidized under similar conditions. The 5,6-quinones (17) can be hydrolyzed by base to the 6-hydroxy-5,8-quinones (18) in high yields. They dimerize to the intermediate 6,6'-biquinazolinyl-5,8-quinones on prolonged heating at 80°–90°C, and these cyclize to form benzofuran derivatives.⁸¹

⁷⁶ H. Meerwein, P. Laasch, R. Mersch, and J. Nentwig, *Chem. Ber.* **89**, 224 (1956).

⁷⁷ J. Lykkeberg and N. A. Klitgaard, *Acta Chem. Scand.* **24**, 2268 (1970).

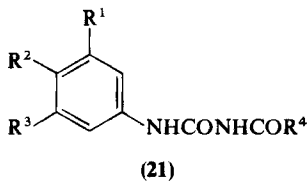
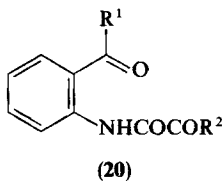
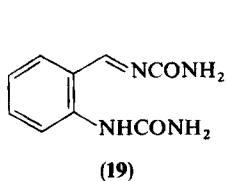
⁷⁸ D. J. Berry and B. J. Wakefield, *J. Chem. Soc. C*, 642 (1971).

⁷⁹ G. J. de Voghel, T. L. Eggerichs, B. Clamot, and H. G. Viehe, *Chimia* **30**, 191 (1976).

⁸⁰ H. G. Viehe, G. J. de Voghel, and F. Smets, *Chimia* **30**, 189 (1976).

⁸¹ N. B. Karpova and Yu. S. Tsizin, *Khim. Geterotsikl. Soedin.*, 1403 (1973).

For the preparation of quinazolines by metathesis, see Section IV,D.



B. QUINAZOLIN-2-ONES

The intermediate in the Gabriel-Posner synthesis of quinazolin-2(1*H*)-one (fusion of *o*-aminobenzaldehyde with excess of urea), was found to be *o*-ureidobenzylidene urea (19), which then cyclized on heating, or in the presence of acid, with elimination of urea. The intermediate reacted with aniline, *N*-methylaniline, and *N,N*-dimethylaniline to form 4-*p*-aminophenyl, 4-*p*-methylanilino, and 4-*p*-dimethylanilino quinazolin-2(1*H*)-ones in an unusual manner.⁸² Several quinazolin-2(1*H*)-ones were prepared by converting *o*-acylanilines into *o*-ureidophenyl ketones followed by cyclization in acetic acid medium for long periods at 55°C.⁸³ A novel modification of this cyclization involved a Curtius or Hofmann reaction on 2'-benzoyloxanilic acid chlorides (20: R² = Cl) or amides (20: R² = NH₂), respectively. The yields in the former reactions were generally higher.⁸⁴ Intramolecular cyclization of *o*-unsubstituted aniline derivatives to give quinazolin-2(1*H*)-ones had never been reported. Recently, however, *N*-phenyl-*N'*-acyl ureas (21) lacking in ortho-substituents in the benzene ring were cyclized to 4-substituted quinazolin-2(1*H*)-ones in polyphosphoric acid at 90°–130°C.⁸⁵ 4-Aminoquinazolin-2(1*H*)-ones were prepared by a Chichibabin reaction (NaNH₂) from quinazolin-2(1*H*)-ones.⁸⁶

C. QUINAZOLIN-4-ONES

Large numbers of quinazolin-4-ones made by standard procedures are found in the patent literature. *o*-Acylaminobenzoic acids were conveniently

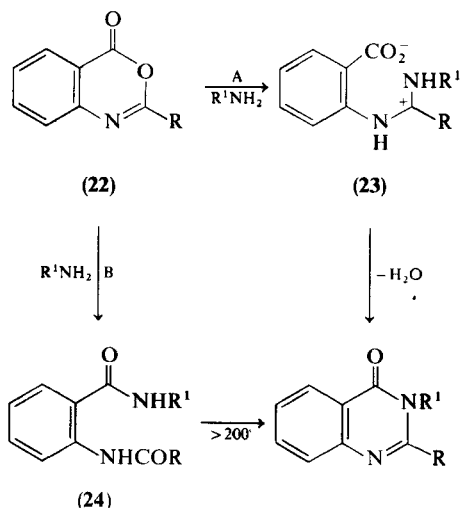
⁸² I. Ya. Postovskii, O. N. Chupakhin, T. L. Pilicheva, N. A. Klyuev, and S. L. Mertsalov, *Zh. Org. Khim.* **11**, 875 (1975) [*CA* **83**, 43265 (1975)].

⁸³ A. Allais and J. Meier, French Patent 1,520,743 (1968) [*CA* **71**, 49975 (1969)].

⁸⁴ K. Ishizumi, S. Inaba, and H. Yamamoto, *J. Org. Chem.* **39**, 2587 (1974).

⁸⁵ P. Lederer, V. Trcka, S. Hynie, and Z. Budesinsky, *Cesk. Farm.* **24**, 201 (1975) [*CA* **84**, 105533 (1976)].

⁸⁶ A. Rosowsky, N. Papathanasopoulos, and E. Modest, *J. Heterocycl. Chem.* **9**, 1449 (1972).



SCHEME 1

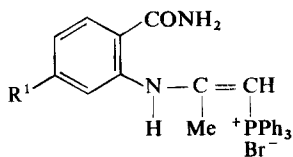
converted into 2,3-benzo-substituted quinazolin-4-ones by heating with the required amine in polyphosphoric acid.^{87,88} Acylanthranils (**22**; 3,1(4*H*)-benzoxazin-4-ones) are still popular starting materials for the syntheses of quinazolin-4-ones. The reaction of acylanthranils with amines was studied in some detail, and two pathways were proposed (Scheme 1). When simple primary amines, e.g., ethylamine and aniline, were used the synthesis proceeded via path A. Secondary amines, or amines with substituents on the α -carbon atom, followed path B. The rates of conversion to compounds **23** and/or **24** varied directly with the pK_a value of the amine, but inversely with steric bulk of the amine. The results demonstrated that both steric and electronic factors were important in determining the overall reactivity by either pathway, but that only the steric factors had a significant effect on the selectivity of the pathway.⁸⁹ 1,3(4*H*)-Benzothiazine-4-thione similarly yielded quinazoline-4(3*H*)-thiones, and two such molecules joined by a 3,3'-polymethylene bridge were formed if ω -diaminoalkanes were used.⁹⁰ As in quinazolin-2(1*H*)-ones, the Chichibabin reaction of quinazolin-4-ones provided 2-aminoquinazolin-4(3*H*)-ones. Quinazoline-4(3*H*)-thione, as expected, reacted similarly in the Chichibabin reaction except that it went

⁸⁷ T. Hisano, K. Shoji, and M. Ichikawa, *Org. Prep. Proced. Int.* **7**, 271 (1975).

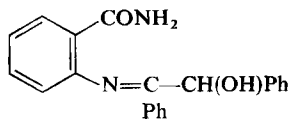
⁸⁸ P. A. Petyunin, Yu. V. Kozhevnikov, and I. S. Berdinskii, *Uch. Zap., Perm'sk. Gos. Univ.* **141**, 309 (1966) [*CA* **69**, 77226 (1968)].

⁸⁹ L. A. Errede, J. J. McBrady, and H. T. Oien, *J. Org. Chem.* **42**, 656 (1977).

⁹⁰ L. Legrand and N. Lozac'h, *Bull. Soc. Chim. Fr.*, 1411 (1975).



(25)



(26)

further and the 4-thione group was substituted giving 2,4-diaminoquinazoline.⁸⁶ *o*-Aminobenzonitriles in hot dimethylformamide containing hydrobromic acid, or acetic acid containing formamide, gave respectively quinazolin-4(3*H*)-ones and 2-methylquinazolin-4(3*H*)-ones. No doubt the 2-carbon atoms were derived from dimethylformamide or acetic acid, respectively. If thioacetamide was added to these solutions quinazoline-4(3*H*)-thiones were formed.⁹¹

2-Methylquinazolin-4(3*H*)-one was obtained in over 62% yield by reacting the phosphorane (25) with sodium hydride in methyl cyanide. The phosphorane was readily formed from anthranilamide and prop-2-ynyltriphenylphosphonium bromide.^{92,93} When anthranilamide was fused with benzoin and a trace of acid at 150°C, it gave 2-phenylquinazolin-4(3*H*)-one together with *o*-*N*-(α -benzoyl benzyl)aminobenzamide. The latter was cyclized, with ethyl orthoformate, to 1-(α -benzoylbenzyl)quinazolin-4-one. If anthranilamide and benzoin were boiled in benzene with azeotropic removal of water, then the Schiff base (26) was formed. This gave 2-phenylquinazolin-4(3*H*)-one and benzoic acid on heating alone at 150°C or with ethyl orthoformate. The mechanism of this reaction is not clear unless a retro-benzoin condensation and oxidation are occurring.⁹⁴

N-Substituted isatoic anhydrides condensed with *S*-methylthioureas to form 1-substituted 2-amino-quinazolin-4-ones in good yields. When *S*-*N,N'*-trimethylthiourea was used, 1,3-disubstituted-2-methylimino-1,2-dihydroquinazolin-4-one was formed.^{95,96}

A new preparative synthesis of 2-arylquinazolin-4(3*H*)-ones, which was reported recently, involved the pyrolysis of Schiff bases derived from 3-amino-1,2,3-benzotriazin-4-one in paraffin oil at ~300°C, or in boiling 1-methylnaphthalene. The yields were as high as 86–100% but failed entirely when *p*-HO-, *p*-O₂N-, and *p*-Me₂N-benzaldehyde, furfural, and pyridine-2-aldehyde were used. The mechanism in Eq. (5) was proposed although the

⁹¹ J. A. Zoltewicz and T. W. Sharpless, *J. Org. Chem.* **32**, 2681 (1967).

⁹² E. E. Schweizer and S. V. DeVoe, *J. Org. Chem.* **40**, 144 (1975).

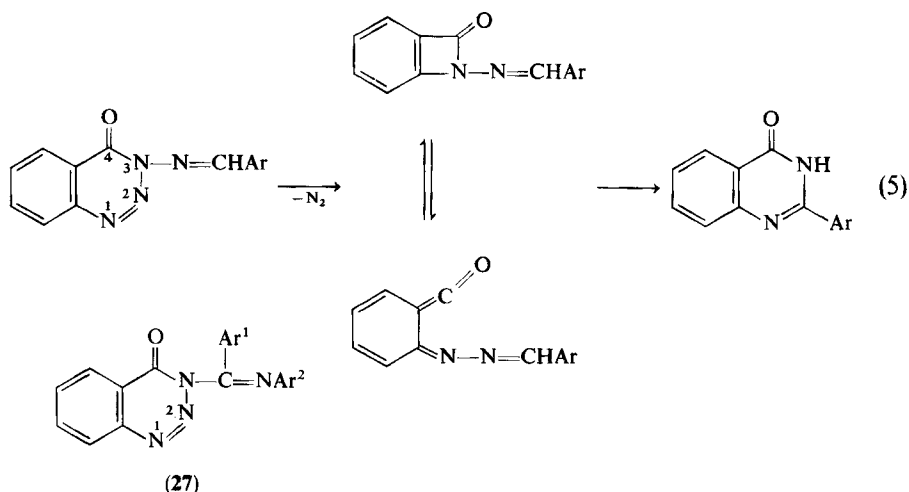
⁹³ E. E. Schweizer, S. DeVoeGoff, and W. P. Murray, *J. Org. Chem.* **42**, 200 (1977).

⁹⁴ A. Mendel, *J. Heterocycl. Chem.* **14**, 153 (1977).

⁹⁵ G. M. Coppola, G. E. Hardtmann, and O. R. Pfister, *J. Org. Chem.* **41**, 825 (1976).

⁹⁶ G. E. Hardtmann, U.S. Patent 3936,453 (1976) [*CA* **84**, 164832 (1976)].

whole process was not clear. An N-N cleavage of the ketene intermediate and a $(4 + 2)\pi$ -cycloaddition reaction are necessary to bring about the transformation.⁹⁷ Similarly N-1 and N-2 were lost as nitrogen in the pyrolysis of the imidoyl derivatives (27), which gave 1,2-diaryl-1,4-dihydroquinazolin-4-ones.^{97a}



D. QUINAZOLINE-2,4-DIONES

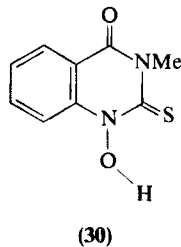
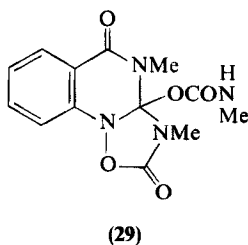
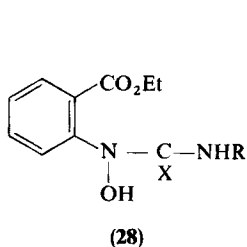
The cyclization of *o*-ureidobenzoic esters to quinazoline-2,4-diones and 4-one-2-thiones, respectively, in aqueous alkali proceeded equally well with the *N*-hydroxy urea ($X = O$) and thiourea ($X = S$) esters 28. If the reagents were altered to triethylamine in pyridine the 2,1-benzisoxazol-3-ones were formed.⁹⁸ Ethyl *o*-hydroxyaminobenzoate reacted with two molecular equivalents of methylisocyanate in ethanolic alkali and gave 3-methyl-1-methylaminocarbonyloxyquinazoline-2,4-dione. When three molecular equivalents were used the tricyclic quinazoline 29 was obtained. A similar reaction with methylisothiocyanate did not behave in the same way, and 3-methylquinazolin-4-one-2-thione was formed. It was shown that the intermediate 1-hydroxy derivative (30) gave 3-methylquinazolin-4-one-2-thione, i.e., loss of the 1-oxygen atom, on further treatment with methylisothiocyanate in the presence of triethylamine.⁹⁹ The preparation of quinazoline-2,4-diones by

⁹⁷ T. McC. Paterson, R. K. Smalley, and H. Suschitzky, *Synthesis*, 187 (1975).

^{97a} T. McC. Paterson, R. K. Smalley, and H. Suschitzky, *Synthesis*, 709 (1975).

⁹⁸ R. Stoffel and H. J. Bresse, *Arch. Pharm. (Weinheim)* **306**, 579 (1973).

⁹⁹ L. Capuano, W. Ebner, and J. Schrepfer, *Chem. Ber.* **103**, 82 (1970).

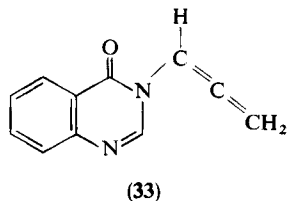
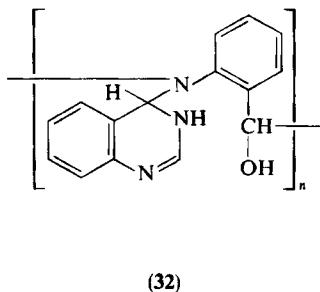
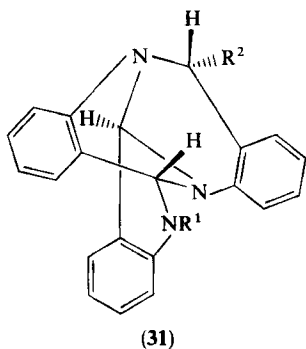


photochemical rearrangement of iminoisatin *N*-oxides is described in Section VII.

IV. Reactions of Quinazolines and Quinazolinones

A. RING-CLEAVAGE REACTIONS

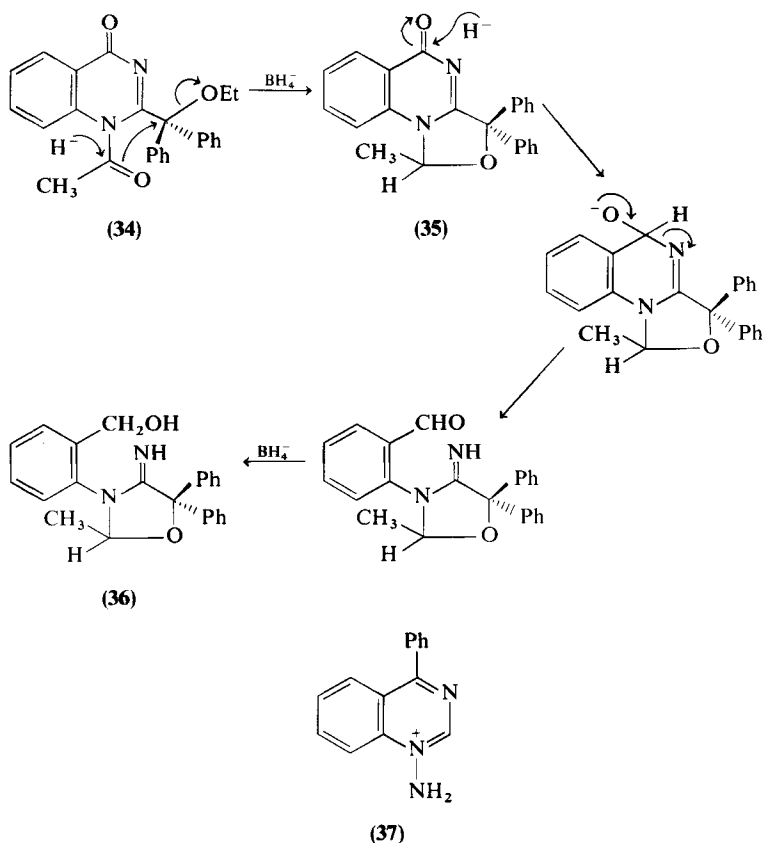
Quinazoline is relatively stable in aqueous solutions over a wide range of pH values. At 90°C, on the other hand, it is degraded and the products that are formed react with each other. Albert and Yamamoto¹⁰⁰ studied the stability of quinazoline at pH values ranging from $H_0 - 4$ to pH 14. They found that in aqueous solution at pH values between 5 and 12 quinazoline was relatively stable, whereas above and below these limits decomposition was extensive. Five main products were isolated and characterized from acidic solutions. These were *o*-aminobenzaldehyde, the anhydro trimer [(31): $R^1 = H$, $R^2 = OH$], the anhydro tetramer [(31): $R^1 = H$; $R^2 = -NHC_6H_4CHO(o)$], the monoformyl tetramer [(31): $R^1 = CHO$; $R^2 = -NHC_6H_4CHO(o)$], and substance Q. Substance Q was shown to be a polymer of the addition



¹⁰⁰ A. Albert and H. Yamamoto, *J. Chem. Soc. C*, 1944 (1968).

product (32) of *o*-aminobenzaldehyde and quinazoline. The percentages of these five compounds that were formed after 1 hour at 90°C in sodium hydrogen sulfate buffer were 30, 31, 9, 6, and 17 at pH 2 and 10, 2, 2, 5.3, and 72 at pH 1.5.

Quinazolin-4(3*H*)-ones are not readily degraded by reagents in alkaline media because they form stable anions. However, if the tautomeric hydrogen is substituted, then the heterocyclic ring becomes susceptible to cleavage. Two such examples are 3-propadienylquinazolin-4-one (33) and 1-acetyl-2-(α -ethoxy- α -phenyl)benzylquinazolin-4-one (34). When the former compound was boiled for 2 hours with sodium in 96% ethanol, nucleophilic attack at C-2 occurred and 2-(2-formamidophenyl)-5-methyloxazole was formed by a subsequent reaction of the olefinic side chain.¹⁰¹ The second



¹⁰¹ C. Bogentoft, Ö. Ericsson, P. Stenberg, and B. Danielsson, *Tetrahedron Lett.*, 4745 (1969).

compound (34) was reduced with sodium borohydride in boiling ethanol to the benzyl alcohol 36, and a mechanism that followed the sequence 34 → 35 → 36 was proposed.¹⁰²

B. ALKYLATION

For many years it was assumed that alkylation of quinazoline with methyl iodide gave only 3-methylquinazolinium iodide. More recently, however, with the aid of proton magnetic resonance, Bunting and Meathrel demonstrated that a mixture of 1-methyl- and 3-methylquinazolinium iodide were formed in the ratio 1:5 by this method.¹⁰³ A phenyl substituent in position 4 directed methylation to N-1.¹⁰⁴ Amination also was directed to N-1, as was shown by the reaction of *O*-mesitylenesulfonyl hydroxylamine with 4-phenylquinazoline, which gave the *N*-amino cation 37.¹⁰⁵ Quinazoline and 2- and 4-phenylquinazoline formed anionic derivatives with sodium in tetrahydrofuran.¹⁰⁶ These anions produced methyl derivatives, on treatment with methyl iodide, which gave some indication of where the negative charges were located in the molecule (see further discussion in Section VI,A).

Alkylation of 2-substituted quinazolin-4(3*H*)-ones by reaction with sodium hydride in dimethylformamide followed by alkylation provided *O*- and *N*-alkyl derivatives. The extent of alkylation at the different sites was reasonably explained in terms of steric properties of the 2-substituents.¹⁰⁷ The silver salt of quinazolin-4(3*H*)-one and tetra-*O*-acetyl-β-D-glucopyranosyl bromide gave a 40% yield of the *O*-glycosyl derivative in contrast with the mercury salt, which gave mainly the *N*-3-glycosyl derivative. As in the alkylation of mercapto compounds, quinazoline-4(3*H*)-thione gave the *S*-glycosyl derivative. If sodium hydroxide was used as base a 56% yield of the *S*-glycosyl derivative was formed together with a small amount (8%) of the *N*-3-glycosylquinazoline-4-thione.¹⁰⁸ α-Bromoketones are also good alkylating agents for oxo heterocycles and quinazolin-4(3*H*)-ones provided 3-acylmethylquinazolin-4-one. In order to obtain the 1-substituted derivatives 4-aminoquinazoline was the obvious compound to alkylate. It reacted with

¹⁰² S. C. Pakrashi and A. K. Chakravarty, *J. Org. Chem.* **39**, 3828 (1974).

¹⁰³ J. W. Bunting and W. G. Meathrel, *Can. J. Chem.* **48**, 3449 (1970).

¹⁰⁴ Y. Yamada, T. Oine, and I. Inoue, *Bull. Chem. Soc. Jpn.* **47**, 343 (1974).

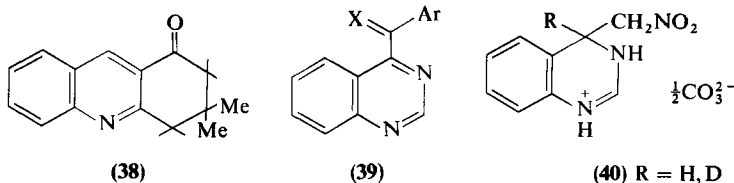
¹⁰⁵ Y. Tamura, Y. Miki, J. Minamikawa, and M. Ikeda, *J. Heterocycl. Chem.* **11**, 675 (1974).

¹⁰⁶ J. G. Smith and J. M. Sheepy, *J. Org. Chem.* **42**, 78 (1977).

¹⁰⁷ C. Bogentoft, L. Kronberg, and B. Danielsson, *Acta Pharm. Suec.* **6**, 489 (1969) [*CA* **72**, 11916 (1970)].

¹⁰⁸ G. Wagner and F. Suess, *Pharmazie* **24**, 35 (1969).

α -bromoketones at N-1, and products were then hydrolyzed by acid or base to N-1 acylmethylquinazolin-4-ones.¹⁰⁹



C. ADDITION REACTIONS

The addition of water (see Section II,B) and other nucleophiles across the 3,4-double bond of quinazoline is well established.^{1,2} More recently other nucleophiles, such as dimedone, have given isolable 3,4-adducts.¹¹⁰ Similarly, malononitrile and other compounds with active methylene groups added across the 3,4-double bond of quinazoline, but in this case the reaction proceeded further with ring opening and formation of 2-amino-3-cyanoquinoline.^{110,111} The dimedone adduct was also made to react further in the presence of alkali to form the acridone **38**.¹¹⁰

Quinazoline behaved like aromatic aldehydes in undergoing benzoin-type condensations in the presence of cyanide ion, which gave 4,4'-biquinazolinyl after oxidation.¹¹² Crossed benzoin-type condensations were performed between quinazoline and several aromatic aldehydes, in the presence of cyanide ions, and provided 4-benzoylquinazolines (**39**: X = O) together with some 4- α -hydroxybenzylquinazolines (**39**: X = H, OH) and 4,4'-biquinazolinyl. The reaction was unsuccessful if strong electron donating or attracting substituents were present in the benzaldehyde.¹¹³

The 3,4-nitromethyl adduct (**40**: R = H) was formed when quinazoline was fused with nitroacetic acid until evolution of carbon dioxide was complete.¹¹⁴ 4-Deuterioquinazoline gave the adduct **40** (R = D) and established that the nucleophile had added on to C-4.

¹⁰⁹ R. S. Sinyak, I. A. Mazur, and P. M. Kochergin, *Khim. Farm. Zh.* **10**, 67 (1976) [*CA* **85**, 63022 (1976)].

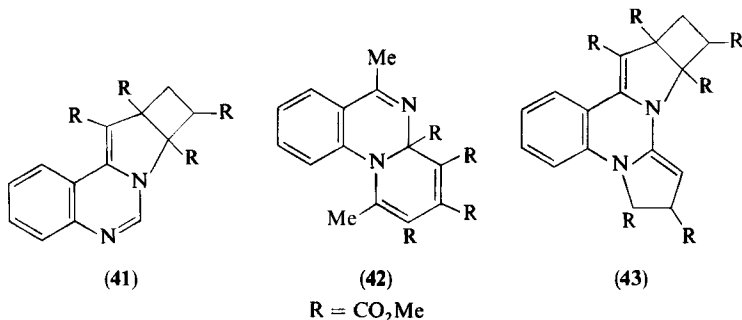
¹¹⁰ A. Albert and W. Pendergast, *J. C. S. Perkin I*, 1794 (1973).

¹¹¹ T. Higashino, H. Ito, and E. Hayashi, *Chem. Pharm. Bull.* **20**, 1544 (1972).

¹¹² W. L. F. Armarego and R. E. Willette, *J. Chem. Soc.*, 1258 (1965).

¹¹³ T. Higashino, M. Goi, and E. Hayashi, *Chem. Pharm. Bull.* **22**, 2493 (1974).

¹¹⁴ W. L. F. Armarego, *J. Chem. Soc. C*, 986 (1969).



Dimethyl acetylenedicarboxylate is a reagent that adds onto a variety of heterocyclic compounds when one or more molar excesses of it are used.¹¹⁵ Quinazolines are no exception. Quinazoline and 2-methylquinazolines did not give crystalline materials, but 4-methyl-, 2,4-dimethyl-,¹¹⁶ 4-ethoxy-, and 4-ethoxy-6-methylquinazolines¹¹⁷ condensed with 2- or 3-molar equivalents of dimethylacetylene dicarboxylate. The 1:2 adducts **41** and **42** of 4-methyl¹¹⁶ and 2,4-dimethylquinazoline,^{116,117} and the 1:3 adduct (**43**) of the latter compound all retain the quinazoline skeleton. 4-Ethoxyquinazoline gave the 1:2 adduct (**44**) which rearranged in the presence of acid to the adduct **46**, presumably via ring cleavage across the C-2, N-3 bond followed by rotation, as in the cation **45**, and ring closure. The PMR spectrum of a solution of the ester **46** containing the chiral shift reagent tris[3-(2,2,2-trifluoro-1-hydroxy-ethylidene)-(+)-camphorato]-europium(III) had two sets of methyl ester resonances. On standing, one set of signals decreased at the expense of the other, and finally only one set remained. The optical rotation of the solution also altered with time before it settled to its final value. This was explained by an asymmetric transformation of the second order (kinetic resolution¹¹⁸) whereby the mixture of two diastereoisomeric complexes is slowly converted into one diastereoisomer. The optical lability of the asymmetric center (starred in **46**) was most probably due to reversible ring opening (cf. **45**).^{117,119}

Quinazoline and 4-methylquinazoline condensed similarly with dimethylketene but gave the 1:4 adducts **47**: R = H, and **47**: R = Me, respectively.¹²⁰

¹¹⁵ R. M. Acheson, *Adv. Heterocycl. Chem.* **1**, 125 (1963); R. M. Acheson and N. F. Elmore, *Adv. Heterocycl. Chem.* **23**, 263 (1978).

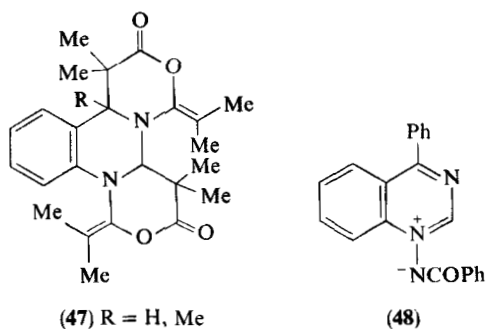
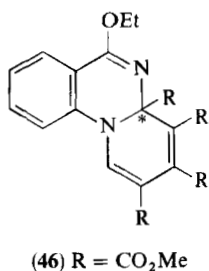
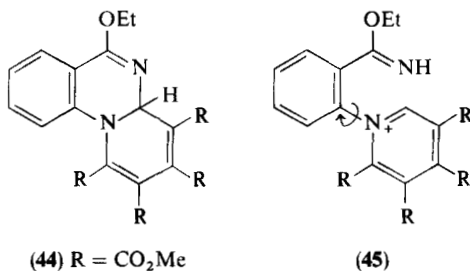
¹¹⁶ R. M. Acheson, M. W. Foxton, and J. K. Stubbs, *J. Chem. Soc. C*, 926 (1968); R. M. Acheson and G. Procter, *J. C. S. Perkin I*, 1924 (1977).

¹¹⁷ P. J. Abbott, R. M. Acheson, M. Y. Kornilov, and J. K. Stubbs, *J. C. S. Perkin I*, 2322 (1975).

¹¹⁸ W. L. F. Armarego, "Stereochemistry of Heterocyclic Compounds. Part 1. Nitrogen Heterocycles," p. 205. Wiley (Interscience), New York, 1977.

¹¹⁹ R. M. Acheson, P. J. Abbott, J. K. Stubbs, and M. Yu. Kornilov, *Khim. Geterotsikl. Soedin.*, 1701 (1975).

¹²⁰ M. A. Shah and G. A. Taylor, *J. Chem. Soc. C*, 1651 (1970).



The ylid **48**, on the other hand, formed 1:1-cycloadducts with acetylenic esters and maleimides.¹²¹

The addition of methyl lithium to 2,4-diphenylquinazoline occurred at the 4-position and produced the respective 4-methyl-2,4-diphenyl-1(3)-lithiodihydroquinazoline, which could be alkylated with methyl iodide to the corresponding 3,4-dimethyl- and 1,4-dimethyl-2,4-diphenyldihydroquinazolines.¹²² These results should be compared with the reductions by sodium followed by alkylation of the anions with methyl iodide (see Section VI,A).

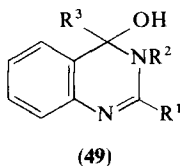
Grignard reagents are known to add across the carbonyl groups of *N*-substituted quinazolinones but are not generally useful reactions because

¹²¹ Y. Tamura, T. Miki, K. Nakamura, and M. Ikeda, *J. Heterocycl. Chem.* **13**, 23 (1976).

¹²² J. G. Smith and J. M. Sheepy, *J. Heterocycl. Chem.* **12**, 231 (1975).

after addition an α -carbinolamine is formed that undergoes ring opening. Recent studies of Grignard additions to quinazolin-4-ones have confirmed this, although there are several instances in which the carbinolamine (e.g., **49**) has been isolated.^{123,124} Quinazoline-2,4-diones also react with Grignard reagents and the hydroxy derivatives formed are less susceptible to ring opening.¹²⁵

The Reformatsky reagent ethyl bromo zinc acetate added across the 3,4-double bond of quinazoline, but oxidation followed and 4-ethoxycarbonylmethylquinazoline was formed in low yields.¹²⁶



D. METATHESIS

The quinazoline molecule is well suited for metathesis reactions, and many derivatives have been prepared in this way. Most of the displacement reactions are by nucleophilic substitution, but a few electrophilic substitution reactions are reported. Substitution in the heterocyclic ring is more facile than in the benzene ring, and the 4-position is usually the most reactive. An exception is the exchange of hydrogen by deuterium in deuterium oxide, which is catalyzed by platinum on asbestos. At 130°C 2-deuterioquinazoline was formed in 80% yield after 5 hours, and further heating at 150°C for 12 hours gave 2,4-dideuterioquinazoline.¹²⁷ The base-catalyzed exchange using sodium deuteroxide in methanol occurred at 50°–80°C, and in this case the exchange rate at C-4 was faster than at C-2.¹²⁸

The kinetics of displacement of chlorine by piperidine from 2- and 4-chloroquinazoline had been correlated with HMO theory,¹²⁹ but great

¹²³ T. Zimaity, M. Anwar, F. I. Abdel-Hay, and M. F. Abdel-Megeid, *Acta Chim. Acad. Sci. Hung.* **87**, 251 (1975).

¹²⁴ M. A. F. Elkaschef, F. M. E. Abdel-Megeid, and A. Abdel-Kader, *Collect. Czech. Chem. Commun.* **39**, 287 (1974).

¹²⁵ F. M. E. Abdel-Megeid, M. A. F. Elkaschef, K. E. Mokhtar, and K. E. M. Zaki, *J. Chem. Soc. C*, 1055 (1971).

¹²⁶ T. Higashino, T. Washizu, and E. Hayashi, *Yakugaku Zasshi* **93**, 1234 (1973).

¹²⁷ G. Fischer and M. Puza, *Synthesis*, 218 (1973).

¹²⁸ I. F. Tupitsyn, N. N. Zatssepina, A. V. Kirova, and A. V. Kapustin, *Reakts. Sposobn. Org. Soedin.* **5**, 601 (1968).

¹²⁹ P. Beltrame, P. L. Beltrame, and M. Simonetta, *Tetrahedron* **24**, 3043 (1968).

caution must be taken in these correlations because these reactions may be more complicated than would appear at first. van der Plas and co-workers have shown that ring opening of the heterocyclic ring occurred when 4-chloroquinazoline reacted with lithium piperidine in piperidine. They observed, by using an ^{15}N label in position 3, that in the reaction of 4-chloroquinazoline with potassium amide in liquid ammonia, 50% of the label at N-3 was absent in the 4-aminoquinazoline formed. Half of the amination reaction had proceeded by substitution and the other half by addition of nucleophile followed by ring opening and ring closing reactions (ANRORC mechanism).¹³⁰ Similarly with the aid of ^{15}N they demonstrated that substitution in 2-chloro-4-phenyl-(3- ^{15}N)quinazoline by potassium amide in liquid ammonia proceeded by an S_{N} [ANRORC] mechanism to the extent of 70%. With ethanolic ammonia at elevated temperatures, on the other hand, the extent of this mechanism was 34–67% depending on the concentration of ammonia. The amination of 2- and 4-chloroquinazoline with ethanolic ammonia also followed the [ANRORC] mechanism to the extent of 31% and 19%, respectively; the rest of the reaction proceeded by direct nucleophilic substitution.¹³¹ This was the first report that an S_{N} [ANRORC] mechanism had taken place in substitution reactions involving ethanolic ammonia. The displacement of halogen in 4-chloro-2-phenylquinazoline by KN^{15}N_2 to form the 4-azido derivative did not involve an S_{N} [ANRORC] mechanism.¹³² 2-Methylquinazoline was formed by an analogous mechanism when 2-bromoquinoline reacted with KNH_2 in liquid ammonia.¹³³

The 4-halogen atom in chloroquinazoline was displaced by aziridine,¹³⁴ by amines (with derivatives of α -amino acids),¹³⁵ and by fluorine (with KHF)^{136,137} more readily than a halogen atom at C-2. When a 4-fluorine atom was activated, as in hexafluoroquinazoline, it could be readily substituted by an amino or methoxy group. Nucleophilic substitution in the benzene ring of quinazoline was also possible. Hexachloroquinazoline gave hexafluoroquinazoline with anhydrous potassium fluoride, and the latter

¹³⁰ J. De Valk, H. C. van der Plas, F. Jansen, and A. Koudijs, *Rec. Trav. Chim. Pays-Bas* **92**, 460 (1973).

¹³¹ A. P. Kroon and H. C. van der Plas, *Rec. Trav. Chim. Pays-Bas* **93**, 227 (1974).

¹³² C. Théas, F. W. Wehrli, and C. Wenstrup, *Helv. Chim. Acta* **59**, 259 (1976).

¹³³ H. J. den Hertog and D. J. Buurman, *Rec. Trav. Chim. Pays-Bas* **86**, 187 (1967).

¹³⁴ G. E. Hardtmann and H. Ott, *J. Org. Chem.* **39**, 3599 (1974).

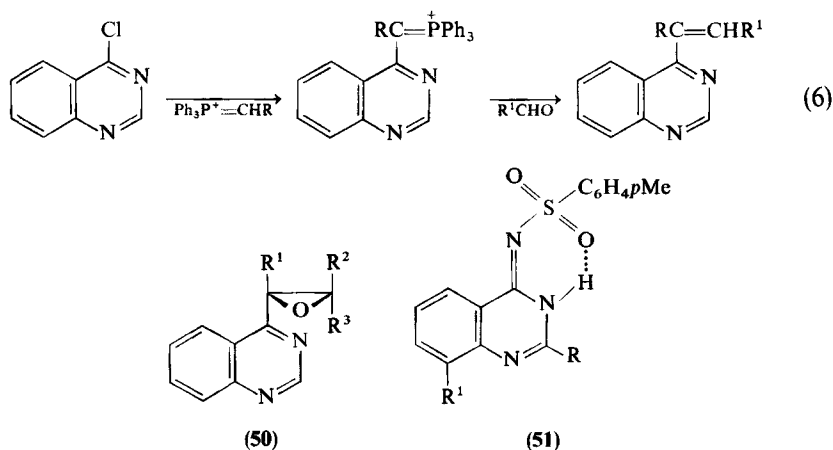
¹³⁵ P. M. Kochergin, I. A. Mazur, and R. S. Sinyak, *USSR, Patent* 446,506 (1974) [*CA* **82**, 43448 (1975)].

¹³⁶ D. M. W. van den Ham, G. F. S. Harrison, A. Spaans, and D. van der Meer, *Rec. Trav. Chim. Pays-Bas* **94**, 168 (1975).

¹³⁷ C. G. Allison, R. D. Chambers, J. A. H. MacBride, and W. K. R. Musgrave, *Tetrahedron Lett.*, 1979 (1970).

produced 4-aminopentafluoroquinazoline and a mixture of 2,4,7-trimethoxy-5,6,8-trifluoro- and 2,4,5,7-tetramethoxy-6,8-difluoroquinazoline with ammonia and sodium methoxide, respectively.¹³⁷ A kinetic study of methoxy-dehalogenation of quinazolines with chlorine and fluorine atoms in the benzene ring showed that the positional order of reactivity was $7 > 5 > 6 > 8$, and that fluorine was displaced more easily than chlorine.¹³⁸

A useful reagent for converting quinazolin-2(1*H*)- and 4(3*H*)-ones into 2- and 4-aminoquinazolines in one step was diphenylphosphordiamide.¹³⁹ An Arbuzov reaction occurred between trialkylphosphite and chloroquinazolines, and dialkyl 4-quinazolinylphosphonates were formed. The 4-chlorine atom was more reactive than the 2-chlorine atom, and the phosphonate group could be displaced by methoxide and amines.^{140,141} In a new procedure for introducing 4-alkenyl substituents in quinazolines (and heterocycles generally), the halogen atom in 4-chloroquinazoline was substituted by an alkylidenephosphorane. The latter was subsequently condensed with aldehydes in the usual Wittig fashion [Eq. (6)].¹⁴² Sulfonium ylides (e.g., $\text{CH}_2 = \text{SR}_2$) reacted similarly with 4-chloroquinazoline and generated the respective 4-quinazolinylmethenylsulfonium ylides, which reacted with carbonyl compounds to provide the respective epoxy derivatives (50). These epoxides rearranged regiospecifically to alkyl or aralkyl 4-quinazolinyl ketones under the influence of lithium diethylamide.¹⁴³



¹³⁸ W. L. F. Armarego and J. I. C. Smith, *J. Chem. Soc. B*, 407 (1968).

¹³⁹ A. Rosowsky and N. Papathanasopoulos, *J. Heterocycl. Chem.* **9**, 1235 (1972).

¹⁴⁰ J. Almog and E. D. Bergmann, *Isr. J. Chem.* **11**, 723 (1973).

¹⁴¹ K. Issleib and H. P. Abicht, *J. Prakt. Chem.* **315**, 649 (1973).

¹⁴² E. C. Taylor and S. F. Martin, *J. Am. Chem. Soc.* **96**, 8095 (1974).

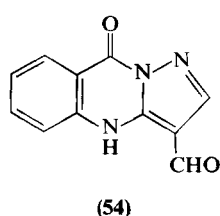
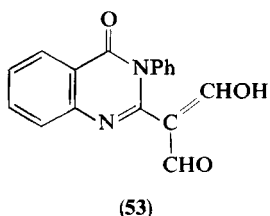
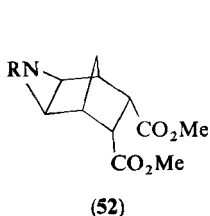
¹⁴³ E. C. Taylor, M. L. Chittenden, and S. F. Martin, *Heterocycles* **1**, 59 (1973).

4-*p*-Tosylquinazoline was readily converted into 4-cyanoquinazoline (KCN, DMF),¹⁴⁴ and 2-fluorosulfonyl- and 4-sulfoquinazolines gave the respective 2- and 4-hydrazinoquinazoline with hydrazine.¹⁴⁵ Displacement of sulfur in quinazoline-4(3*H*)-thiones was effected with *p*-tosylisothiocyanate in dioxane which yielded the corresponding 4-*p*-tosylimino-3,4-dihydroquinazolines (51).¹⁴⁶

The oxidative displacement of hydrazine from 4-hydrazinoquinazoline to form quinazoline was brought about with aqueous copper sulfate or oxygen in ethanolic alkali.¹⁴⁷ This reaction can be usefully adapted for the preparation of deuterated derivatives if deuterated solvents are used.

The kinetics of deamination of 4-aminoquinazoline to quinazolin-4(3*H*)-one was studied in detail at various potassium hydroxide concentrations. In 0.05–1.0 *M* potassium hydroxide the rate was first-order with respect to both the amine and hydroxide ion concentration, but in 1.0–3.0 *M* potassium hydroxide the rate increased more rapidly than was expected from a first-order dependence on the hydroxide ion concentration.¹⁴⁸

Further examples have appeared in which N-3 of quinazolin-4-one was exchanged with amino groups from amines. 6,8-Dichloroquinazolin-4(3*H*)-one reacted with amphetamine to generate 13% of 6,8-dichloro-3(1-methyl-2-phenylethyl)quinazolin-4-one; and when it was treated with ethanolamine it produced 6,8-dichloro-3-2'-hydroxyethylquinazolin-4-one and 6-chloro-8-2'-hydroxyethylaminoquinazolin-4-one in 21% and 13% yields, respectively.¹⁴⁹



E. MISCELLANEOUS

Lead tetraacetate oxidized 3-amino-2-methylquinazolin-4-one to the 3-nitrene derivative in dichloromethane. In the presence of dimethyl *endo-cis*-

¹⁴⁴ E. Hayashi, N. Shimada, and A. Miyashita, *Yakugaku Zasshi* **96**, 1370 (1976).

¹⁴⁵ D. J. Brown and J. A. Hoskins, *Aust. J. Chem.* **25**, 2641 (1972).

¹⁴⁶ W. Ried, B. Heine, W. Merkel, and N. Kothe, *Synthesis*, 534 (1976).

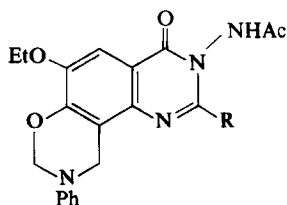
¹⁴⁷ A. Albert and G. Catterall, *J. Chem. Soc. C*, 1533 (1967).

¹⁴⁸ E. Kalatzis, *J. Chem. Soc. B*, 96 (1969).

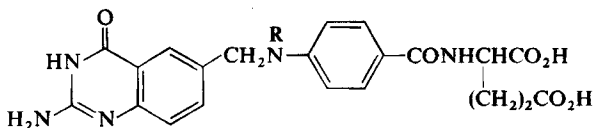
¹⁴⁹ L. J. Chinn, *J. Heterocycl. Chem.* **10**, 403 (1973).

bicyclo[2.2.1]hept-2-ene-5,6-dicarboxylate, the nitrene added across the double bond and gave the adduct (**52**: R = 2-methylquinazolin-4-on-3-yl) in 5–6% yield together with 2-methylquinazolin-4(3*H*)-one (24%). When the olefin was absent from the reaction medium, the latter product was formed in 80% yield.¹⁵⁰

The methyl group in 2-methylquinazolin-4-ones which were substituted on N-3 was shown to undergo the Vilsmeier–Haack reaction. Under these conditions 2-methyl-3-phenylquinazolin-4-one gave the dialdehyde **53** from which a variety of condensed systems could be prepared. 3-Amino-2-methylquinazolin-4-one reacted similarly, but one of the aldehyde groups of the condensation product cyclized with the 3-amino substituent to form the pyrazoloquinazolinone **54**.¹⁵¹ Hydroxymethylation of the benzene ring in quinazolin-4-ones was possible if a hydroxy group was in the carbocyclic ring. Thus 2-substituted 3-acetamido-5-ethoxyquinazolin-4-ones undergo the Mannich reaction with aniline and formaldehyde, and generate oxazinoquinazolinones (e.g., **55**).¹⁵²



(55)



(56)

The reactivity of the amino group in diethyl *p*-aminobenzoylglutamate toward the benzylic carbon atom in 2-amino-6-bromomethylquinazolin-4(3*H*)-one had provided a new route to quinazoline analogs of folic acid (**56**).¹⁵³

V. Quinazoline *N*-Oxides

Oxidation of quinazoline with hydrogen peroxide usually yields quinazolin-4(3*H*)-one because the 3,4-hydrate [see Eq. (4)] is oxidized faster than the anhydrous species. More recently, quinazoline was oxidized with hydrogen peroxide in the presence of catalytic amounts of sodium tungstate and gave a mixture of quinazolin-4(3*H*)-one, quinazoline-3-oxide, and the pre-

¹⁵⁰ G. R. Meyer and N. A. Rao, *J. Heterocycl. Chem.* **14**, 335 (1977).

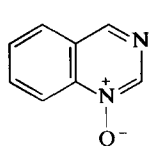
¹⁵¹ R. S. Pandit and S. Seshadri, *Indian J. Chem.* **11**, 532 (1973).

¹⁵² G. Kumar, B. Lal, P. Singh, and A. P. Bhaduri, *Indian J. Chem.* **14B**, 133 (1976).

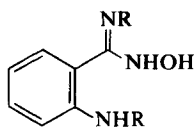
¹⁵³ S. P. Acharya and J. B. Hynes, *J. Heterocycl. Chem.* **12**, 1283 (1975).

vously unknown quinazoline-1-oxide (57). The last two were isolated in 7% and 5.5% yields, respectively, by TLC.¹⁵⁴

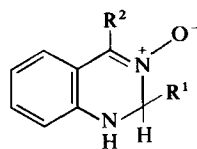
Further confirmation that *syn*-*o*-aminobenzaldehyde oximes are converted into 3,1,4-benzoxadiazepines and the *anti*-isomers into quinazoline 3-oxides in boiling triethyl orthoformate was demonstrated with the methoxy derivatives.³⁸ *o*-Aminobenzaldehyde oxime in acetic anhydride containing hydrogen chloride gave, after 6 days at room temperature, 2-methylquinazoline 3-oxide, not 2-methyl-3,1,4-benzoxazepine. The structure of 2-methylquinazoline 3-oxide was established by an X-ray analysis.¹⁵⁵ 2-Substituted quinazoline 3-oxides have been prepared by condensation of *o*-aminobenzaldehyde oximes and iminoether salts in methanol,¹⁵⁶ and from 2-amido-4,5-dimethoxyacetophenone *O*-benzoyloximes and dry hydrogen chloride.¹⁵⁷ The diacyl derivatives (58: R = COR') of the iminohydroxamic acids were similarly cyclized on acylation to 2-substituted 4-aminoquinazoline 3-oxides.¹⁵⁸ When the hydroxamic acid 58 (R = H) was treated with *p*-methoxybenzaldehyde or cinnamaldehyde in a 1:1 ratio 2-substituted 4-hydroxyimino-1,2,3,4-tetrahydroquinazolines were formed, whereas when the ratio was 1:2 the oxadiazolo-quinazolines were obtained. Propionaldehyde, butyraldehyde, phenylacetaldehyde, benzaldehyde, *m*- and *p*-nitro and chloro benzaldehydes, and the acid 58 (R = H), on the other hand, produced 2-substituted-4-amino-1,2-dihydroquinazoline 3-oxides (59: R² = NH₂) only, regardless of the molar ratios.¹⁵⁹



(57)



(58)



(59)

cis-2-Amino-5-chlorobenzophenone oxime reacted with dimethyl acetylene dicarboxylate to form 6-chloro-2-methoxycarbonyl-2-methoxycarbonylmethyl-4-phenyl-1,2-dihydroquinazoline 3-oxide. The *trans*-oxime also reacted but did not give a heterocyclic compound.¹⁶⁰ The crystalline product

¹⁵⁴ Y. Kobayashi, I. Kumadaki, H. Sato, Y. Sekine, and T. Hara, *Chem. Pharm. Bull.* **22**, 2097 (1975).

¹⁵⁵ L. Golic, V. Kaucic, B. Stanovnik, and M. Tisler, *Tetrahedron Lett.*, 4301 (1975).

¹⁵⁶ P. D. Sorrentino, British Patent 1,201,626 (1970) [*CA* **73**, 120661 (1970)].

¹⁵⁷ H. Zenno, S. Umio, T. Kamitani, K. Kariyone, H. Yazawa, and T. Ogino, Japanese Patent 7,000,499 (1970) [*CA* **72**, 90506 (1970)].

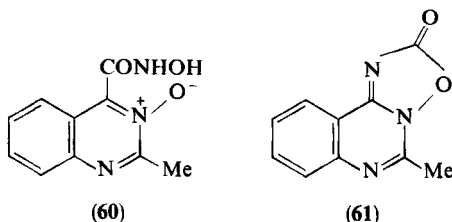
¹⁵⁸ H. Goncalves, F. Mathis, and C. Foulcher, *Bull. Soc. Chim. Fr.*, 2599 (1970).

¹⁵⁹ H. Goncalves, C. Foulcher, and F. Mathis, *Bull. Soc. Chim. Fr.*, 2615 (1970).

¹⁶⁰ J. B. Hester, *J. Org. Chem.* **39**, 2137 (1974).

obtained from mixing *o*-aminoacetophenone and methazonic acid turned out to be 4-methyl-2-nitromethyl-1,2-dihydroquinazoline 3-oxide (**59**; $R^1 = \text{CH}_2\text{NO}_2$; $R^2 = \text{Me}$). This dihydro compound eliminated nitromethane on melting and formed 4-methylquinazoline 3-oxide.¹⁶¹

An earlier proposed structure for the bis oxime of *N*-acetylisanin was shown to be erroneous. The correct structure (**60**) was deduced from its chemical reactions and by synthesis from methyl *o*-*N*-acetamidobenzoylformate and hydroxylamine.¹⁶² The hydroxamic acid (**60**) underwent a Lossen reaction to form the 4-isocyanato derivative, which cyclized to the oxadiazoloquinazoline **61**. The structure of the latter was confirmed by an X-ray analysis.¹⁶³



o-Amidinobenzonitriles (**13**), which were useful intermediates for the preparation of 4-aminoquinazolines (with NH_4OAc ; Section III,A), also produced 4-aminoquinazoline 3-oxides in high yields by reaction with hydroxylamine.⁷⁵ Hydroxylamine *O*-sulfonic acid, a useful reagent for preparing *N*-amino heterocycles (e.g., **37**), reacted with certain quinazolines in a different manner. Quinazoline and its 2-methyl derivative gave the respective 4-sulfoxyamino-3,4-dihydroquinazolines together with products from ring cleavage and ring contraction, whereas 4-methylquinazoline gave a 25% yield of 4-methylquinazoline 3-oxide. Clearly hydroxylamine-*O*-sulfonic acid added across the 3,4-double bond of 4-methylquinazoline, but this was followed by a rearrangement and by elimination of the SO_3H group.¹⁶⁴

Methylation of 4-aminoquinazoline 3-oxide, prepared from 4-methoxyquinazoline and hydroxylamine, produced a 1:1 mixture of 4-imino-3-methoxy-3,4-dihydroquinazoline (19%) and 3-methoxy-4-methylimino-3,4-dihydroquinazoline (18%). These were reduced with Raney nickel to 4-amino- and 4-methylaminoquinazoline, respectively.¹⁶⁵

¹⁶¹ W. L. F. Armarego, T. J. Batterham, K. Schofield, and R. S. Theobald, *J. Chem. Soc. C*, 1433 (1966).

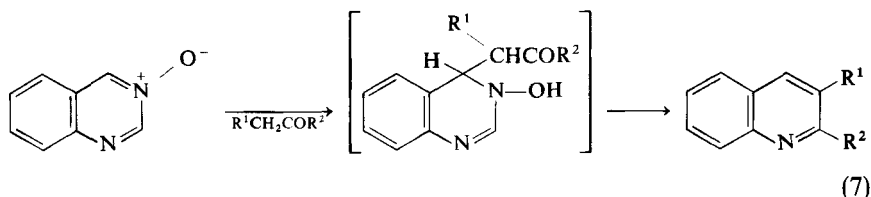
¹⁶² J. Bergman, R. Carlsson, and J. O. Linderström, *Tetrahedron Lett.*, 3611 (1976).

¹⁶³ J. Bergman, J. O. Linderström, J. Abrahamsson, and E. Hadler, *Tetrahedron Lett.*, 3615 (1976).

¹⁶⁴ K. Kasuga, M. Hirobe, and T. Okamoto, *Yakugaku Zasshi* **94**, 945 (1974).

¹⁶⁵ E. Hayashi, T. Higashino, and S. Tomisaka, *Yakugaku Zasshi* **87**, 578 (1967).

The addition of Michael reagents to quinazoline 3-oxide was studied in great detail by Higashino, Hayashi, and their collaborators. Ketones with an α -methylene group, in the absence of a base, added across the 3,4-double bond of quinazoline 3-oxide, but the reaction proceeded further; ring cleavage, elimination of hydroxylamine, and the 2-carbon atom followed, and the corresponding 2,3-disubstituted quinolines were obtained [Eq. (7)]. The yields of the quinolines, however, were poor.¹⁶⁶ Similarly malononitrile, phenylacetone, and cyanoacetic ester gave the respective 3-substituted-2-aminoquinolines. Ethyl malonate, on the other hand, did not cause ring cleavage and produced 4-ethoxycarbonylmethylquinazoline.¹⁶⁷



Quinazoline 3-oxides are known to undergo ring expansion upon irradiation with UV light, but this is not always the case (see Section VII,C). Quinazoline 3-oxide and its 7-methoxy derivative simply rearranged to the corresponding quinazolin-4(3*H*)-ones on photolysis.³⁸ 6-Chloro-4-phenylquinazoline 3-oxides that possess the following substituents at C-2: CH₂Cl, CH₂I, CH₂OAc, CH₂OBz and CH₂SEt, were also sensitive to ultraviolet light and diffuse sunlight, but they underwent ring contraction and provided 6-chloro-2-phenylbenzoxazole.¹⁶⁸ The 2-chloromethyl, 2-iodomethyl, and 2-dichloromethyl derivatives reacted with hydroxylamine in ethanol at room temperature and afforded the same 6-chloro-2-hydroxyiminomethyl-4-phenylquinazoline 3-oxide in 30, 50, and 70% yields, respectively. An oxidation must have occurred in the first two reactions in order to form the aldehyde oxime.¹⁶⁹

3-Hydroxyquinazolin-4-ones (**62**), which are tautomers of 4-hydroxyquinazoline 3-oxides (see also **3**, Section II,A), were useful catalysts for peptide synthesis when dicyclohexylcarbodiimide was used. They decreased the amount of racemization of α -amino acids during formation of the peptide bond. They are not, however, as effective as 3-hydroxy-1,2,3-benzotriazin-4-one.^{170,171}

¹⁶⁶ T. Higashino, K. Suzuki, and E. Hayashi, *Chem. Pharm. Bull.* **23**, 746 (1975).

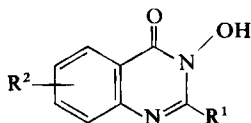
¹⁶⁷ T. Higashino, Y. Nagano, and E. Hayashi, *Chem. Pharm. Bull.* **21**, 1943 (1973).

¹⁶⁸ K. H. Wünsch and H. Bajdala, *Z. Chem.* **10**, 144 (1970).

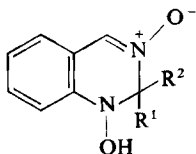
¹⁶⁹ J. Dusemund, *Arch. Pharm. (Weinheim)* **307**, 883 (1974).

¹⁷⁰ W. König and R. Geiger, *Chem. Ber.* **103**, 2024 (1970).

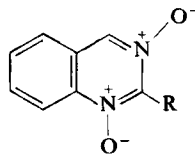
¹⁷¹ W. Koenig, R. Geiger, and H. Wissman, German Patent 2,202,613 (1973) [*CA* **79**, 137510 (1973)].



(62)



(63)



(64)

4-Methylquinazoline 3-oxide was one of the heterocyclic bases used to obtain a linear ΔH° - pK_a relationship. For this purpose its thermodynamic parameters (ΔG° , ΔH° , and ΔS°) for ionization were determined accurately.¹⁷²

A general synthesis of quinazoline 1,3-dioxides and their 1,2-dihydro derivatives was devised by Taylor and Bartulin. In this synthesis *o*-hydroxylaminobenzaldehyde oxime condensed with aldehydes and ketones to yield 2,2-disubstituted 1,2-dihydro-1-hydroxyquinazoline 3-oxides (63). When the dihydro compounds (63: $R^1 = H$) derived from aldehydes or from formaldehyde were oxidized with chloranil, benzoquinone, or mercuric oxide, 2-substituted quinazoline 1,3-dioxides (64) and the parent quinazoline 1,3-dioxide (63: $R = H$) were produced.¹⁷³

The ^{14}N chemical shifts of quinazoline 1-oxide, 3-oxide, and 1,3-dioxide were reported and were correlated with π -charge densities at the *N*-oxide nitrogen atom calculated by the MO-SCF-PPP method.¹⁷⁴

For molecular rearrangements involving quinazoline *N*-oxide, see Section VII.

VI. Reduced Quinazolines

Quinazolinones and thiones are not considered as hydro compounds in this section unless other double bonds in the rings are saturated. 4-Methylene-3,4-dihydroquinazolines, however, are included in this section.

A. 1,2-, 1,4-, AND 3,4-DIHYDROQUINAZOLINES

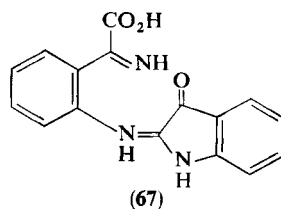
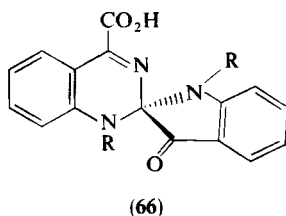
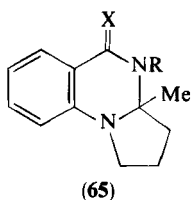
A new ring closure to quinazolines was found by allowing 2-benzoyl-5-nitroaniline to react with hexamine (hexamethylenetetramine), in the presence of ethyl α -bromoacetate, in a solvent. When the solvent was methanol,

¹⁷² M. J. Cook, N. L. Dassanyake, C. D. Johnson, A. R. Katritzky, and T. W. Toone, *J.C.S. Perkin II*, 1069 (1974).

¹⁷³ E. C. Taylor and J. Bartulin, U.S. Patent 3,476,756 (1969) [*CA* 72, 43718 (1970)].

¹⁷⁴ L. Stefaniak, *Spectrochim. Acta, Part A* 32, 345 (1976).

ethanol, or water, the product was 1-methoxymethyl-, 1-ethoxymethyl-, or 1-hydroxymethyl-1,2-dihydro-5-nitro-4-phenylquinazoline, respectively. It was intriguing that similar reactions with 2-benzoyl-5-chloroaniline gave only 6-chloro-4-phenylquinazoline.¹⁷⁵ In another ring closure, *o*-amino-benzamides were condensed with 5-chloropentan-2-one in boiling toluene and provided several 3-substituted 2-methyl-1,2-trimethylene-1,2-dihydroquinazolin-4-ones (**65**; X = O). The intermediates in this synthesis may well be 2-*ω*-chloropropyl-2-methyl-1,2-dihydroquinazolin-4-ones.¹⁷⁶ 1,2-Dihydroquinazolin-4-ones have also been prepared by reduction of the corresponding quinazolin-4-ones with sodium borohydride. It is important that the tautomeric hydrogen atom is substituted for this reaction to proceed, otherwise the anion, which is resistant toward reduction, is produced. When 3-aryl-2-methylquinazolin-4-ones were reduced with NaBH₄, overreduction occurred and *o*-ethylaminobenzanilides were formed. If the hydrochlorides, however, were used, then reduction took place without ring cleavage and the products were 3-aryl-2-methyl-1,2-dihydroquinazolines. Quaternization of N-1, as in 3-aryl-1-ethyl-2-methyl-4-oxoquinazolinium iodide, facilitated the reduction to the 1,2-dihydroquinazolin-4-ones.^{177,178} These dihydroquinazolinones yield the starting materials on oxidation with potassium permanganate¹⁷⁷ or mercuric EDTA.¹⁷⁹



The red crystalline product, called isamic acid,¹⁸⁰ from treatment of isatin with ammonia, was proved by Cornforth¹⁸¹ to be the *spiro*-1,2-dihydroquinazolin-4-carboxylic acid **66** (R = H). *N*-Methylisatin provided the dimethyl derivative (**66**; R = Me). Isamic acid has an asymmetric carbon atom and is chiral. In an attempted optical resolution, its brucine salt gave

¹⁷⁵ N. Blazevic, M. Oklobdzija, V. Sunjic, F. Kajfez, and D. Kolbah, *Arch. Pharm. Jugosl.* **25**, 223 (1975) [*CA* **84**, 121762 (1976)].

¹⁷⁶ F. Gatta and R. Landi Vittory, *Gazz. Chim. Ital.* **99**, 715 (1969).

¹⁷⁷ K. Okumura, T. Oine, Y. Yamada, G. Hayashi, and M. Nakama, *J. Med. Chem.* **11**, 348 (1968).

¹⁷⁸ K. Okumura, T. Oine, Y. Yamada, G. Hayashi, M. Nakama, and T. Nose, *J. Med. Chem.* **11**, 788 (1968).

¹⁷⁹ H. Möhrle and C. M. Seidel, *Arch. Pharm. (Weinheim)* **309**, 572 (1976).

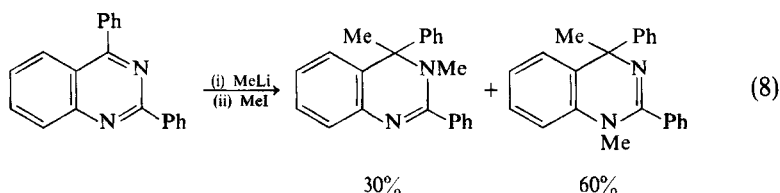
¹⁸⁰ P. de Mayo and J. J. Ryan, *Chem. Commun.*, 88 (1967).

¹⁸¹ J. W. Cornforth, *J.C.S. Perkin I*, 2004 (1976); G. F. Field, *Chem. Commun.*, 886 (1969).

one pure diastereoisomeric salt in 64% yield (128% of "theoretical"), indicating that an asymmetric transformation of the second order (kinetic resolution—see Section IV,C) had occurred. This was borne out by the instability of the free optically active acid, which racemized at the rate of 8% per day in methanol. The optical instability was probably due to ring-chain tautomerism via the intermediate (67). The color and very weak basicity had been attributed to *spiroconjugation*.¹⁸¹

2-(2-Pyridyl)-3-(*N*-2-picolylimino)-1,2-dihydroquinazolin-4-one formed stable complexes with Zn, Cd, Mn, Cu, Co, and Ni ions. Infrared (IR) studies indicated that the metals coordinated with two different conformations of this ligand.¹⁸²

1,4-Dihydroquinazolines are in equilibrium with 3,4-dihydroquinazolines, which are generally thermodynamically more stable. In order to obtain 1,4-dihydroquinazolines it is necessary to have a substituent at N-1 so as to freeze the tautomerism. The proportion of 1*H*-1,4-hydroquinazoline produced in a kinetically controlled reaction can, however, be appreciable. This is demonstrated in the following reactions. 4-Phenylquinazoline was reduced with sodium in tetrahydrofuran to the monomeric dianion. When the dianion was treated with water or one equivalent of methyl iodide, only 4-phenyl- and 4-methyl-4-phenyl- 3,4-dihydroquinazolines were isolated. If, however, two molecular equivalents of methyl iodide were added, a mixture of 1,4-dimethyl-4-phenyl- (16%) and 3,4-dimethyl-4-phenyl- (42%) 3,4-dihydroquinazolines was formed.¹⁰⁶ The monomeric dianion of 2,4-diphenylquinazoline gave 1,4-dimethyl-2,4-diphenyl- and 3,4-dimethyl-2,4-diphenyl-3,4-dihydroquinazoline in 60% and 27% yields, respectively, with methyl iodide. If ethyl chloroformate was used as alkylating agent, on the other hand, an 85% yield of 1,4-bisethoxycarbonyl-2,4-diphenyl-3,4-dihydroquinazoline was formed.¹⁸³ A similar behavior was observed when methyl lithium reacted with 2,4-diphenylquinazoline followed by methylation of the intermediate lithium salts [Eq. (8)].¹²²

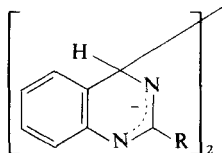


Monomeric dianions were formed when 4-phenyl- and 2,4-diphenylquinazolines were treated with sodium in tetrahydrofuran (see above). Quin-

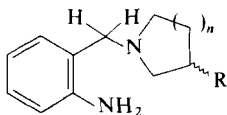
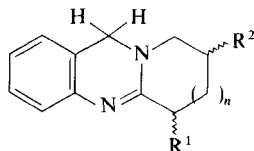
¹⁸² C. Pelizzi and G. Pelizzi, *Gazz. Chim. Ital.* **105**, 7 (1975).

¹⁸³ J. G. Smith, J. M. Sheepy, and E. M. Levi, *J. Org. Chem.* **41**, 497 (1976).

azoline and 2-phenylquinazoline were also reduced under the same conditions but gave dimeric dianions (**68**). These were hydrolyzed with water to 3,4,3',4'-tetrahydro-4,4'-biquinazoliny and its 2,2'-diphenyl derivative, which could be oxidized by oxygen at low temperatures to the respective 4,4'-biquinazolinyls. Addition of methyl iodide to the dianions gave *N*-methyl derivatives.¹⁰⁶



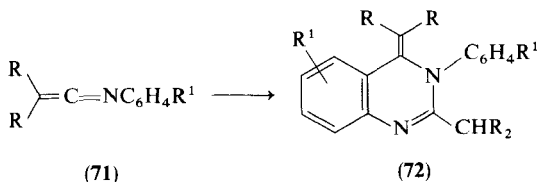
(68) R = H, Ph

(69) $n = 1, 2, \text{ or } 3$; R = H, OH

(70)

The preparation of 3,4-dihydroquinazolines from *o*-aminobenzylamines is still an attractive method of synthesis.^{184,185} A useful adaptation of this basic idea was the oxidation of **69** with mercuric ions in the presence of EDTA.¹⁸⁶ The yields of products (**70**) were better than 50% when eight oxidation equivalents were used. The oxidation was regioselective with compounds **69** ($n = 1$; R = OH) and **69** ($n = 2$; R = OH) which gave almost exclusively (**70**: $n = 0$; R¹ = OH; R² = H; i.e., *d,l*-vasicine) and (**70**: $n = 1$; R¹ = H; R² = OH), respectively. The cyclization most probably involved a cyclic iminium intermediate.¹⁸⁷

Several 4-substituted 3-methyl-3,4-dihydroquinazolines were obtained by addition of nucleophilic bases across the 3,4 double bond of the 3-methyl-quinazolinium cation,¹⁸⁸ and carbon nucleophiles (e.g., acetyl acetone) added across the 3-4 double bond of 3-phenyl-2-oxo(or thio)-(1*H*)-quinazolinium salts in much the same way.¹⁸⁹



(71)

(72)

¹⁸⁴ E. P. Papadopoulos and B. George, *J. Org. Chem.* **42**, 2530 (1977).

¹⁸⁵ M. R. Boots, S. G. Boots, and D. E. Moreland, *J. Med. Chem.* **13**, 144 (1970).

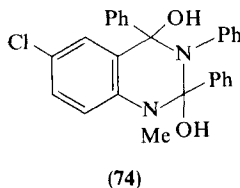
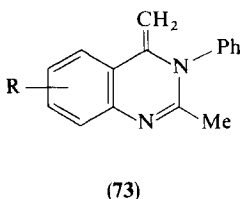
¹⁸⁶ H. Möhrle and P. Gundlach, *Tetrahedron Lett.*, 997 (1970).

¹⁸⁷ H. Möhrle and P. Gundlach, *Arch. Pharm. (Weinheim)* **306**, 541 (1973).

¹⁸⁸ T. L. Pilicheva, O. N. Chupakhin, and I. Ya. Postovskii, *Khim. Geterotsikl. Soedin.*, 561 (1975).

¹⁸⁹ K. Lempert and P. Gyulai, *Tetrahedron* **26**, 3443 (1970).

Two syntheses involving cycloaddition reactions were the self-condensation of *N*-aryltrichloroacetimido chlorides, in the presence of antimony pentachloride, which gave 45–63% yields of 3-aryl-2,4-bis(trichloromethyl)-3,4-dihydroquinazolines,¹⁹⁰ and the dimerization of *N*-aryl dialkylketenimines (**71**).¹⁹¹ The imines **71**, in the latter reaction, required a temperature of 125°C for several days to give the 4-methylene-3,4-dihydroquinazolines (**72**) in ca. 50% yields. Quinazolines could not be formed in this reaction when both the ortho positions of the *N*-aryl group were substituted.



Ring cleavage caused by the addition of Grignard reagents to quinazolin-4(3*H*)-ones has been mentioned earlier (Section IV,C). This cleavage does not occur readily with quinazoline-2,4-diones, however. Thus methyl magnesium bromide reacted with 3-phenylquinazoline-2,4-diones and gave 4-methylene-2-methyl-3-phenyl-3,4-dihydroquinazolines (**73**). Ethyl magnesium bromide gave a similar product, but *p*-methoxyphenyl magnesium bromide produced 4-hydroxy-2,4-bis-*p*-methoxyphenyl-3-phenyl-3,4-dihydroquinazoline, because unlike the alkyl reagents this product cannot be dehydrated without forming a quinazolinium salt. The addition followed a different course when both N-1 and N-3 were substituted; for example, 6-chloro-1-methyl-3-phenylquinazoline-2,4-dione furnished 6-chloro-2,4-dihydroxy-1-methyl-2,3,4-triphenyl-1,2,3,4-tetrahydroquinazoline (**74**). If N-1 and N-3 were unsubstituted, then dehydration occurred readily, as in the conversion of quinazoline-2,4(1*H*,3*H*)-dione into 2,4-diphenyl- and 2,4-diethylquinazolines with phenyl and ethyl magnesium bromide respectively.¹²⁵

3,4-Dihydroquinazolines have been formed by the acid- or base-catalyzed disproportionation of 4-alkoxy(or hydroxy)-3-phenyl-3,4-dihydroquinazolin-2(1*H*)-thiones(or -ones). These gave a mixture of 3-phenylquinazolin-4-one-2(1*H*)-thione(or -one) and 3-phenyl-3,4-dihydroquinazolin-2(1*H*)-thione(or -one). The disproportionation is akin to a Cannizzaro reaction.¹⁹²

¹⁹⁰ R. R. Schmidt, *Tetrahedron Lett.*, 3443 (1968).

¹⁹¹ M. W. Barker and J. D. Rosamond, *J. Heterocycl. Chem.* **11**, 241 (1974).

¹⁹² K. Lempert and P. Gyulai, *Z. Chem.* **10**, 384 (1970).

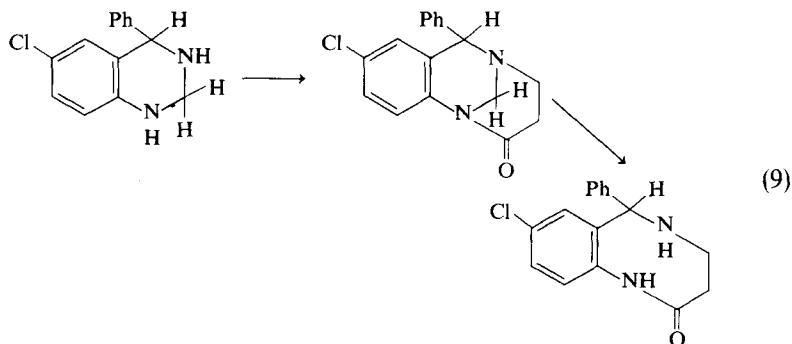
3,4-Dihydroquinazolines unsubstituted at N-3 have been oxidized to the respective quinazolines with chlorine or bromine in alkaline medium.¹⁹³

In a study of the mechanism of methoxyaminolysis of cyclic amidines, it was found that no methoxyaminolysis of 3,4-dihydroquinazoline and 1-methyl-1,4-dihydroquinazoline occurred in a phosphate buffer at pH 7.9 and 50°C. After long periods, only products of hydrolysis were formed.¹⁹⁴

B. TETRA-, HEXA-, AND OCTAHYDROQUINAZOLINES

Quaternization of the pyrimidine ring of quinazolines enhances its reactivity toward nucleophiles. This reactivity has been used to advantage for preparing 1,2,3,4-tetrahydro derivatives. Methylation of 4-phenylquinazoline occurred at N-1 and N-3 (7:1) and was the first example in which it was shown that alkylating at two different sites in quinazolines was possible. The 1-methyl-(and 3-methyl)quinazolinium salt that was formed was reduced with sodium borohydride to 1-methyl-(and 3-methyl)-4-phenyl-1,2,3,4-tetrahydroquinazoline.¹⁹⁵ Potassium permanganate oxidized the latter compound to 1-methyl-4-phenylquinazolin-2(1*H*)-one.

Heavily substituted 1,2-dihydroquinazolin-4-ones were reduced with lithium aluminum hydride to 1,2,3,4-tetrahydroquinazolines without reductive cleavage of the heterocyclic ring. Several 1,2,3,4-tetrahydroquinazolines (65: X = H₂) were prepared in this way, and their structures were confirmed by syntheses from *o*-substituted aminomethylanilines and 5-chloropentan-2-one.¹⁷⁶



¹⁹³ M. Yamamoto, S. Morooka, M. Koshiba, S. Inaba, and H. Yamamoto, Japanese Patent 76 08,287 (1976) [*CA* **84**, 180277 (1976)].

¹⁹⁴ B. A. Burdick, P. A. Benkovic, and S. J. Benkovic, *J. Am. Chem. Soc.* **99**, 5716 (1977).

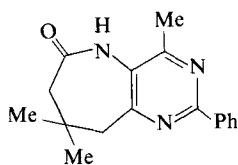
¹⁹⁵ H. Ott and M. Denzer, *J. Org. Chem.* **33**, 4263 (1968).

1,2,3,4-Tetrahydroquinazolines were useful for the preparation of 1,5-benzodiazocines in a novel approach whereby N-1 and N-3 were bridged with a stable linkage and the 2-carbon atom was removed as formaldehyde by hydrolysis [Eq. (9)] or hydrogenolysis.¹⁹⁶

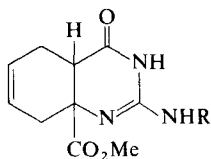
The 8-methylene carbon atom in 5,6,7,8-tetrahydroquinazoline was activated by the pyrimidine ring, and reacted with formamide and phosphoryl chloride (a Vilsmeier reagent) to form 8-formamidomethylene-5,6,7,8-tetrahydroquinazoline.¹⁹⁷ The latter was also obtained as a by-product in the synthesis of 5,6,7,8-tetrahydroquinazoline from cyclohexanone and trisformamidomethane.¹⁹⁸ 2-Phenyl-5,6,7,8-tetrahydroquinazoline-4(3*H*)-thione was synthesized from 1-morpholinocyclohex-1-ene and benzoylisothiocyanate. The thione group underwent the usual metathesis reactions.¹⁹⁹ 2-Methyl-5,6,7,8-tetrahydroquinazoline-4(3*H*)-thione was oxidized with potassium permanganate to 2-methyl-4-sulfo-5,6,7,8-tetrahydroquinazoline, which provided 2-methyl-5,6,7,8-tetrahydroquinazolin-4(3*H*)-one on hydrolysis.¹⁴⁵

Hydrazoic acid (Schmidt reaction) caused expansion of the carbocyclic ring of 4,7,7-trimethyl-2-phenyl-5-oxo-5,6,7,8-tetrahydroquinazoline in a regiospecific manner and gave the fused azepinone **75**.²⁰⁰

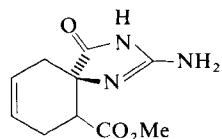
Tetraacetone urea, which was prepared by the acid-catalyzed reaction of diacetone alcohol and urea, was shown to be 4,4,5,5,7-pentamethyl-3,4,4a,5-tetrahydroquinazolin-2(1*H*)-one.²⁰¹



(75)



(76)



(77)

An approach toward the synthesis of simple analogs of tetrodotoxin (**115**) (see also Sections VI,C and VIII) involved a Diels–Alder reaction between a butadiene and a pyrimidine derivative. Thus, butadiene and methyl orotate

¹⁹⁶ M. Denzer and H. Ott, *J. Org. Chem.* **34**, 183 (1969).

¹⁹⁷ T. Koyama, T. Hirota, C. Basho, Y. Watanabe, Y. Kitauchi, U. Satoh, S. Ohmori, and M. Yamato, *Chem. Pharm. Bull.* **24**, 1459 (1976).

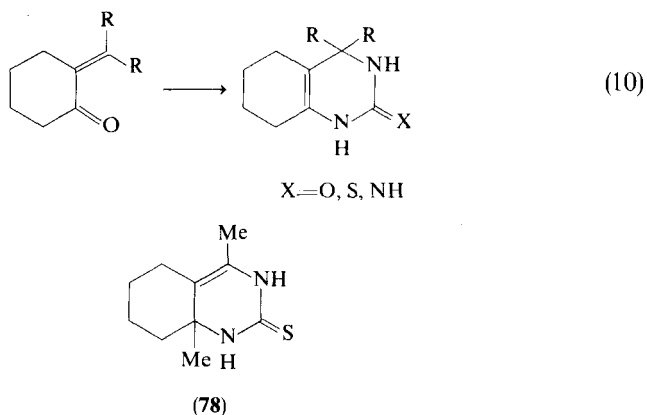
¹⁹⁸ W. L. F. Armarego and T. Kobayashi, *J. Chem. Soc. C*, 1635 (1969).

¹⁹⁹ R. W. J. Carney, H. M. Blatter, and G. De Stevens, U.S. Patent 3 322,759 (1967) [*CA* **68**, 87308 (1968)].

²⁰⁰ A. Ya. Strakov, D. Zicane, D. Brutane, and M. Opmane, *Nov. Issled. Obl. Khim. Khim. Tekhnol., Mater. Nauchno-Tekh. Konf. Professorsko-Prepod. Sostava Nauchn. Rab. Khim. Fak. RPI*, 23 (1973) [*CA* **82**, 4195 (1975)].

²⁰¹ B. R. Statham and I. M. Downie, *Loughborough Univ. Technol., Dep. Chem., Summ. Final Year Stud. Proj. Theses* **10**, 161 (1969) [*CA* **73**, 25396 (1970)].

gave 8a-methoxycarbonyl-4a,5,8,8a-tetrahydroquinazoline-2,4(1*H*,3*H*)-dione, presumably with a *cis* configuration at the ring junctions. The 2-*O*-ethyl derivative did not yield the required 2-amino derivative (**76**), but underwent ring contraction to the *spiro*-imidazolinone **77**. The structure of the latter was confirmed by X-ray analysis. The 2-amino derivatives **76** were then prepared by Diels–Alder reactions between butadienes and 2-amino-6-methoxycarbonylpyrimidin-4(1*H*)-ones.²⁰²



3,4,5,6,7,8-Hexahydroquinazolines were conveniently prepared by condensing 2-alkylidenecyclohexanones with ureas, thioureas, or guanidines [Eq. (10)].^{203,204} The tautomeric 4,8a-dimethyl-3,5,6,7,8,8a-hexahydroquinazoline-2(1*H*)-thione (**78**), however, was obtained from the reaction of 2-acetyl-1-methylcyclohex-1-ene and ammonium isothiocyanate.²⁰³ Catalytic reduction of 5,6,7,8-tetrahydroquinazolines with Pd/C in the presence of acid ceased after absorption of 1 mol equivalent of hydrogen, and gave 3,4,5,6,7,8-hexahydroquinazoline as the hydrochloride. The hexahydro compound, in chloroform solution, was slowly oxidized by air to the starting material. It was readily degraded to 2-formamidomethylcyclohexanone in alkaline solution.²⁰⁵ The catalytic reduction (PtO₂-AcOH) of 2-amino-4-carboxy-5,6,7,8-tetrahydroquinazoline and 4-carboxy-5,6,7,8-tetrahydroquinazolin-2(1*H*)-one (or their methyl esters) similarly occurred across the 3,4 double bond, and gave the corresponding 3,4,5,6,7,8-hexahydroquinazolines. The latter were formed from a kinetically controlled reaction

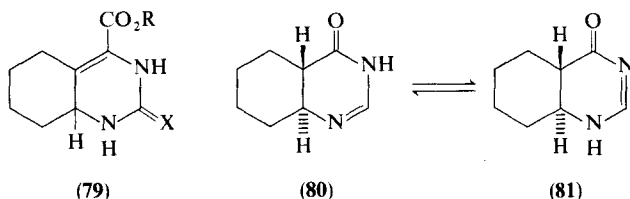
²⁰² J. F. W. Keana, J. S. Bland, P. E. Eckler, V. Nelson, and J. Z. Gougoutas, *J. Org. Chem.* **41**, 2124 (1976).

²⁰³ W. Wendelin, A. Harler, and A. Fuchsgruber, *Monatsh. Chem.* **107**, 141 (1976).

²⁰⁴ G. Jaenecke, *Z. Chem.* **8**, 383 (1968).

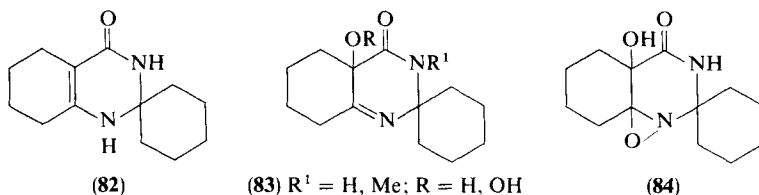
²⁰⁵ W. L. F. Armarego and T. Kobayashi, *J. Chem. Soc. C*, 238 (1971).

because on standing in an acidic medium they rearranged to the thermodynamically more stable 3,5,6,7,8,8a-hexahydroquinazoline tautomers (**79**). The esters rearranged more slowly than the acids.²⁰⁶



The UV spectrum of *trans*-4a,5,6,7,8,8a-hexahydroquinazolin-4(1*H* and 3*H*)-one in aqueous buffer at pH 9.2 was compared with those of the corresponding 1-methyl and 3-methyl derivatives. The spectra clearly indicated that the unsubstituted compound was a tautomeric mixture of **80** and **81** in the ratio 4:1.²⁰⁵ This tautomeric ratio is not very different from that found in quinazolin-4(1*H* and 3*H*)-one (see Armarego,² p. 103). The 4a*S*,8a*S*(-)-enantiomer of hexahydroquinazolinone (**80**) \rightleftharpoons (**81**) was synthesized from 1*S*,2*S*(+)-*trans*-2-aminocyclohexanecarboxamide, of known absolute configuration, and ethyl orthoformate. It had a strong (-)-ve Cotton effect at 264 nm.¹⁹⁸

The difference in *pK_a* values ($\Delta 0.25$ unit) between *cis*- and *trans*-4a,5,6,7,8,8a-hexahydroquinazoline-2,4(1*H*,3*H*)-dione was small but significant.²⁰⁷ A detailed PMR study of these isomers, in trifluoroacetic acid-deuterium oxide solution, showed that the *trans*-isomer was in a rigid conformation whereas the *cis*-isomer consisted of about equal populations of two conformers (see also below).²⁰⁸



The product from heating cyclohexanone and urea was shown to be the 2-*spiro*-1,2,5,6,7,8-hexahydroquinazolin-4(3*H*)-one **82**, not cyclohexylidene-2-carbamoylcyclohex-1-enylamine as was previously proposed. The quin-

²⁰⁶ W. L. F. Armarego and B. A. Milloy, *J.C.S. Perkin I*, 2814 (1973).

²⁰⁷ I. G. Pozharliev and K. Zakharieva, *Izv. Otd. Khim. Nauki, Bulg. Akad. Nauk.* **2**, 341 (1969) [*CA* **72**, 78121 (1970)].

²⁰⁸ A. R. Katritzky, M. R. Nesbit, B. J. Kurtev, M. Lyapova, and I. G. Pojarlieff, *Tetrahedron* **25**, 3807 (1969).

azolinone **82** and its 3-methyl derivative gave the 4a-hydroperoxide **83** (R = OH) on standing in chloroform solution. Reduction of the hydroperoxide with zinc in ethanol provided the 4a-hydroxy derivative (**83**: R = H), but with platinum oxide and hydrogen in ethanol the 4a-hydroxyoctahydroquinazolinone (presumably *cis* C-4a and C-8a) was obtained.²⁰⁹ Oxidation of **82** with hydrogen peroxide or monoperphthalic acid gave the 4a-hydroxy derivative, but the 1,8a-double bond was also attacked to form the oxaziridinooctahydroquinazolinone **84**. Alkali cleaved the 4a,8a-bond, and ferrous sulfate caused a deep-seated rearrangement.²¹⁰

cis- and *trans*-3,4,4a,5,6,7,8,8a-Octahydroquinazolines were prepared from the respective *cis*- and *trans*-2-aminomethylcyclohexylamines and ethyl orthoformate. The hydrochloride salts were stable (amidinium resonance), but the free bases were readily hydrolyzed to the formamido derivatives of the starting material. Surprisingly, *trans*-decahydroquinazoline monoacetate in chloroform was dehydrogenated to *trans*-3,4,4a,5,6,7,8,8a-octahydroquinazolinium chloride when shaken with platinum oxide and hydrogen. The same starting materials were used to make the octahydroquinazolin-2(1*H*)-ones and 2(1*H*)-thiones, and with *S*-methylisothiuronium sulfate they produced the *cis*- and *trans*-2-aminooctahydroquinazolines.²⁰⁵ By using optically active *cis*- and *trans*-2-aminomethylcyclohexylamine, all four enantiomers, 4a*S*,8a*R*(+)-*trans*-, 4a*R*,8a*S*(-)-*trans*-, 4a*S*,8a*S*(-)-*cis*-, and 4a*R*,8a*R*(+)-*cis*-2-amino-3,4,4a,5,6,7,8,8a-octahydroquinazolinium sulfate were prepared with known absolute configurations. They all had plain optical rotatory dispersion (ORD) curves.²¹¹ *N*-Alkyl derivatives of *cis*- and *trans*-2-aminomethylcyclohexylamine gave the corresponding *N*-alkyl-3,4,4a,5,6,7,8,8a-octahydroquinazolin-2(1*H*)-ones by reaction with phosgene in aqueous alkali,²¹²⁻²¹⁴ and these could be converted into the respective 2-aminooctahydroquinazolines with phosphorus oxychloride followed by sodium in liquid ammonia.^{212,213} The *trans*-fused octahydroquinazolines are conformationally rigid, but the *cis*-isomers are mobile, and an equilibrium exists between the conformations **85** and **86**. The PMR spectra of all the *cis*-octahydroquinazolines in which R¹ was H indicated that the predominant conformer was **85**, as shown by the coupling constants of the signals from the two 4-protons.^{205,212-215} In 1-methyl-, 1,3-dimethyl-, and 1-benzyl-*cis*-3,4,4a,5,6,7,8,8a-octahydroquinazolin-2(1*H*)-one, the PMR spectra showed

²⁰⁹ F. Zigeuner and G. Gübitz, *Monatsh. Chem.* **101**, 1547 (1970).

²¹⁰ C. Bischoff, *J. Prakt. Chem.* **318**, 848 (1976).

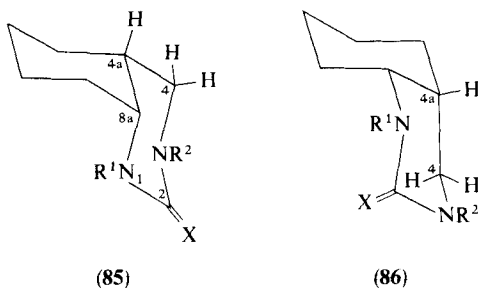
²¹¹ W. L. F. Armarego and T. Kobayashi, *J. Chem. Soc. C*, 1597 (1970).

²¹² W. L. F. Armarego and P. A. Reece, *J.C.S. Perkin I*, 2313 (1974).

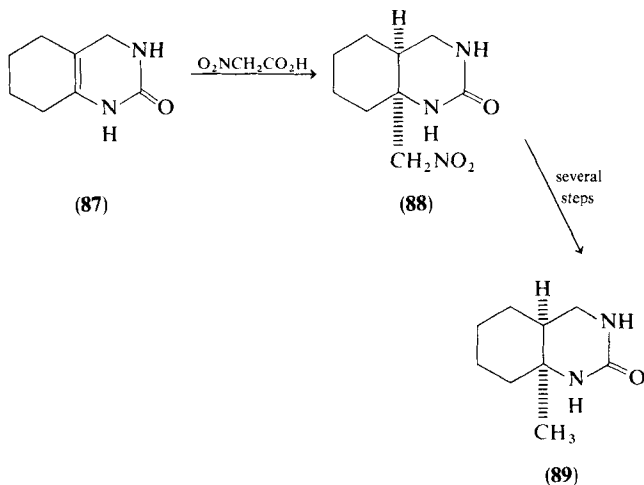
²¹³ W. L. F. Armarego and P. A. Reece, *J.C.S. Perkin I*, 1470 (1975).

²¹⁴ W. L. F. Armarego, *J. Chem. Soc. C*, 1812 (1971).

²¹⁵ W. L. F. Armarego and T. Kobayashi, *J. Chem. Soc. C*, 3222 (1971).

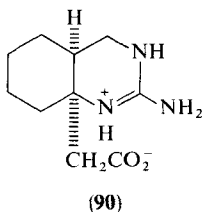


that the major conformer in solution was **86**. The destabilization of conformer **85** in these examples is probably caused by unfavorable nonbonded interactions between the 1-substituent and protons in the carbocyclic ring.²¹² *Trans*- and *cis*- (in the conformation **85**) octahydroquinazolines can be distinguished from each other by the broad and narrow band envelopes, respectively, of the carbocyclic protons in the PMR spectra.^{205,212,215}



Reduction of 5,6,7,8-tetrahydroquinazolin-2(1*H*)-one with sodium borohydride gave 3,4,5,6,7,8-hexahydroquinazolin-2(1*H*)-one (**87**) in high yield. When this hexahydro compound was fused with nitroacetic acid a stereospecific *cis* addition of the elements of nitromethane occurred and the 8a-nitromethyl adduct **88** was formed in quantitative yield. The stereospecificity was deduced by converting **88** into **89** which was synthesized from *cis*-1-methyl-1,2,3,6-tetrahydrophthalic anhydride in several steps without affecting the known stereochemistry of the chiral centers.²¹⁴ The related 8a-aminomethyl-3,4,4a,5,6,7,8,8a-octahydroquinazolin-2(1*H*)-one

was converted into the 8a-bromomethyl derivative, which readily gave the 8a-cyanomethyl compound when treated with potassium cyanide. The latter reaction is of interest because of the known sluggish reactivity of neopentyl halides toward nucleophiles. The cyanomethyl compound was then transformed into the zwitterion **90** in an endeavor to make a simple analog of tetrodotoxin (**115**) (see above).²¹³



C. DECAHYDROQUINAZOLINES

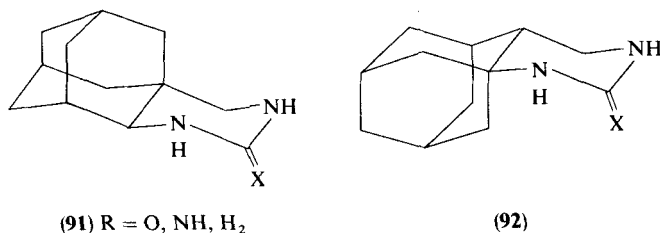
cis- and *trans*-Decahydroquinazolines have been synthesized from *cis*- and *trans*-2-aminomethylcyclohexylamine and formaldehyde. The PMR spectrum of the *cis*-isomer indicated that the conformation similar to **85** ($X = H_2$) predominated. The AB quartet of signals from the C-2 protons coalesced at ca. $160 \pm 4^\circ$ inferring dynamic equilibrium, whereas the spectrum of the *trans*-isomer was unchanged at this temperature. Here also the band envelope from the carbocyclic protons of the *cis*-isomer ($W_{1/2} = 15$ Hz) was much narrower than in the *trans*-isomer ($W_{1/2} = 57$ Hz).¹⁹⁸ All four enantiomers of decahydroquinazoline, viz. 4a*S*,8a*S*(-)-*cis*-, 4a*R*,8a*R*(+)-*cis*-, 4a*S*,8a*R*(+)-*trans*-,²¹¹ and 4a*R*,8a*S*(-)-*trans*-,¹⁹⁸ were synthesized from the respective chiral 2-aminomethylcyclohexylamines of known absolute configuration.

1-Methyl and 1,3-dimethyl-*cis*-decahydroquinazoline, unlike 3-methyl,²¹² 4a-methyl, and 8a-methyl-*cis*-decahydroquinazoline,²¹⁴ exist (in $CDCl_3$) predominantly in the conformation **86** ($X = H_2$). Here also the 1-methyl group must destabilize the generally favored conformation **85** ($X = H_2$) by nonbonded interactions with protons in the carbocyclic ring.

The conformations of the nitrogen lone-pair of electrons (axial or equatorial) on N-1 and N-3 in *trans*-decahydroquinazoline, and its 1-methyl, 3-methyl, and 1,3-dimethyl derivatives were deduced from the relative chemical shifts and coupling constants of the C-2 protons in the PMR spectra.²¹⁶ Later studies of the dipole moments of these quinazolines demonstrated that these deductions were partly fortuitous, and that extreme

²¹⁶ W. L. F. Armarego and T. Kobayashi, *J. Chem. Soc. C*, 2502 (1971).

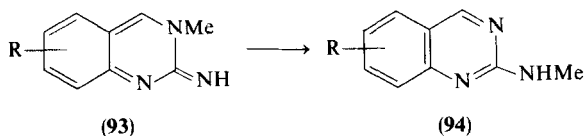
caution must be exerted in interpreting the conformation of the nitrogen lone-pair from the coupling constants of the vicinal protons.²¹⁷



Adamantane derivatives of decahydroquinazoline **91** and **92**, which in essence contain both the *cis*- and *trans*-decahydroquinazoline skeletons in the same molecule, were synthesized with the aim of mimicking some of the biological activity of tetrodotoxin (**115**).^{218,219}

VII. Molecular Rearrangements and Ring Transformations Involving Quinazolines

Molecular rearrangements in which quinazolines are the reactants or the products are discussed in this section. The section is divided into three parts according to the effect that the rearrangement, or ring transformation, has on the size of the heterocyclic ring.



A. REARRANGEMENTS WITHOUT ALTERATION OF RING SIZE

The Dimroth rearrangement of iminoquinazolinones and thiones has been known for some time (see Armarego,² p. 335), and more recently Brown and co-workers have examined the rates of rearrangement of iminoquinazolines which lack an oxo or thio group in the pyrimidine ring. 2-Imino-3-methyl-2,3-dihydroquinazolines (**93**) (prepared by direct methylation of

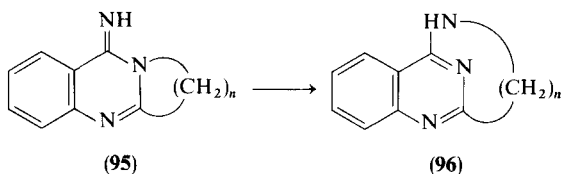
²¹⁷ W. L. F. Armarego, R. A. Y. Jones, A. R. Katritzky, D. M. Read, and R. Scattergood, *Aust. J. Chem.* **28**, 2323 (1975).

²¹⁸ W. L. F. Armarego and P. G. Tucker, *Aust. J. Chem.*, **31**, 1769 (1978).

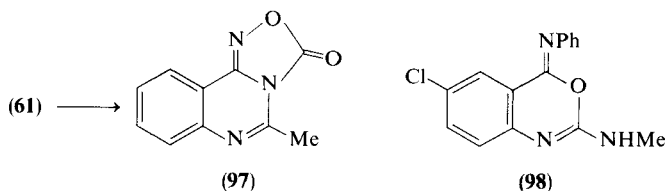
²¹⁹ J. K. Chakrabarti and S. S. Szinaï, U.S. Patent 2,833,653 (1974) [*CA* **83**, 58863 (1975)].

2-aminoquinazolines) rearranged at pH values above 12 into their respective 2-methylaminoquinazolines (**94**). The half-lives of these rates at 25°C and pH 12.5 were: **93**; R = H, 5-OMe, 6-OMe, and 7-OMe; 81, 8.0, 235, and 307 min, respectively; but they were relatively faster (<0.5, 4.8, 5.2, and 264 min) at pH 14.0. The first compound rearranged as rapidly as the parent compound (2-imino-3-methyl-2,3-dihydropyrimidine), and methoxy groups in the benzene ring decreased the rate, except for the 5-methoxy group, which is in a *peri* position with respect to the H-4. These data are consistent with nucleophilic attack at C-4 as an initial step for the rearrangement.²²⁰

4-Imino-3-methyl-3,4-dihydroquinazoline rearranged to 4-methylaminoquinazoline at a slower rate than the 2-imino isomer (i.e., $t_{1/2}$ 4.8 min at pH 13 and 70°C), and here also a 5-methyl group increased the rate con-



siderably. The rearrangement of 2,3-bridged-4-imino derivatives **95** into the amino-bridged products **96** was similarly investigated. When n was 7 and 9, the half-lives of conversion were 185 and 124 min (at 70°C, pH 13); when n was 6 some rearrangement took place, but considerable hydrolysis of **95** ($n = 6$) to the corresponding 2,3-bridged quinazolin-4-one occurred. In compound **95** ($n = 5$) hydrolysis was the only reaction.²²¹ 4-Imino-3-methyl-3,4,5,6,7,8-octahydroquinazoline rearranged to 4-methylamino-5,6,7,8-tetrahydroquinazoline with $t_{1/2} = 3.6$ min (pH 13) at 70°C, but was too slow to measure at 20°C.²²² The isomerization of the oxadiazolone **61** to **97** with alkali can be classified as a Dimroth rearrangement. The structure of **61** has been confirmed by X-ray analysis, and **97** was prepared from 4-hydroxyimino-2-methyl-3,4-dihydroquinazoline and phosgene.¹⁶³



²²⁰ D. J. Brown and B. T. England, *Aust. J. Chem.* **21**, 2813 (1968).

²²¹ D. J. Brown and K. Ienaga, *J.C.S. Perkin I*, 2182 (1975).

²²² D. J. Brown and K. Ienaga, *J.C.S. Perkin I*, 372 (1974).

Related rearrangements in which a nitrogen and oxygen atom, instead of two nitrogen atoms, exchange places are known. 2-Phenylimino-1,2-dihydro-3,1(4*H*)-benzoxazin-4-one rearranged to 3-phenylquinazoline-2,4(1*H*)-dione.²²³ The 4-phenyliminobenzoxazine **98** gave 6-chloro-2-methylamino-3-phenylquinazolin-4-one on melting, but when it was treated with boron trifluoride the rearrangement took a different course and 3-methyl-4-phenylimino-3,4-dihydroquinazolin-2(1*H*)-one was obtained.²²⁴ The intramolecular rearrangement of isoindolo[2,1-*b*]quinazoline-5,11-dione into isoindolo[1,2-*b*]quinazoline-10,12-dione on heating was essentially a transfer of an acyl group from N-1 to N-3 of quinazolin-4-one.²²⁵

The complete transfer of a methyl group from N-1 to N-3 in 2-phenylquinazolin-4-one was brought about at 300°C and was used as evidence for the greater stability of the 4(3*H*)-one tautomer compared with the 4(1*H*)-one tautomer.²²⁶ Migration of a methyl group also occurred in 2-*o*-aminophenyl-1-methylquinazolin-4-one, but not onto the same ring. In this case 2-*o*-methylaminophenylquinazolin-4(3*H*)-one was formed in the acid-induced rearrangement.²²⁷ An oxygen atom was transferred in the conversion of 4-hydroxy-3-methyl-3,4-dihydroquinazoline into 3-methyl-3,4-dihydroquinazolin-2(1*H*)-one by refluxing a toluene or dimethylformamide solution, and on melting.²²⁸

4-*N*-Aziridinylquinazolines rearranged to 2,3-dihydroimidazo[1,2-*c*]quinazolines under the influence of sodium iodide [Eq. (11)]. The iodide ion no doubt acted as a nucleophile which caused cleavage of the aziridinyl ring. This reaction possesses high, but not complete, stereospecificity. The *cis*-dimethyl aziridine (**99**: R¹ = R² = Me; R³ = H), *trans*-**99** (R¹ = R³ = Me; R² = H) and *cis*-**99** (R¹ = R² = Ph; R³ = H) gave the *cis*-**100** (R¹ = R² = Me; R³ = H) (94%), *trans*-**100** (R¹ = R³ = Me; R² = H) (96%), and a mixture of *cis*-**100** (R¹ = R² = Ph; R³ = H) and *trans*-**100** (R¹ = R³ = Ph; R² = H) (68:32%) imidazoquinazolines (Eq. 11).²²⁹

Ultraviolet irradiation of hexafluorocinnoline at 100°C produced a 5–10% yield of hexafluoroquinazoline. An intermediate diazabenzvalene was postulated to account for the rearrangement.²³⁰ The photochemical isomerization of 2-methylcinnolinium-4-olates, but not thiolates or 1-methylcinnol-4(1*H*)-

²²³ M. Kurihara and N. Yoda, *Bull. Chem. Soc. Jpn.* **39**, 1942 (1966).

²²⁴ W. Metlesics, G. Silverman, and L. H. Sternbach, *Monatsh. Chem.* **98**, 633 (1967).

²²⁵ M. Kurihara, *J. Org. Chem.* **34**, 2123 (1969).

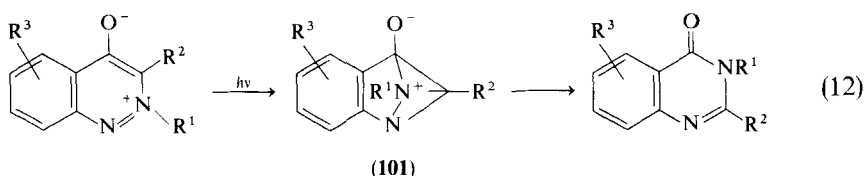
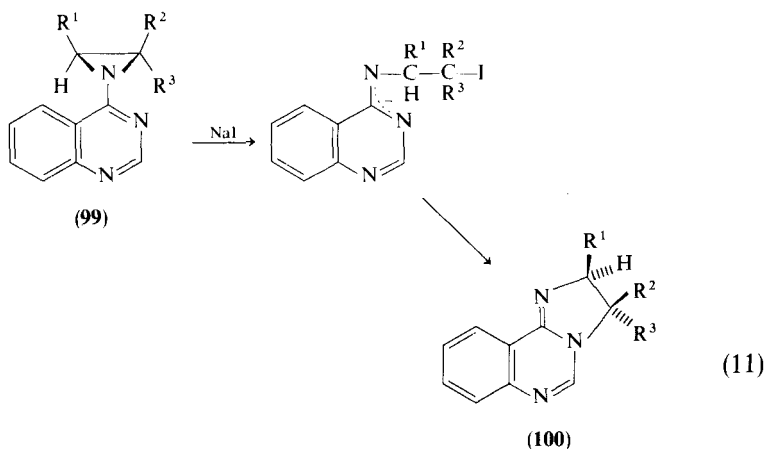
²²⁶ Y. Hagiwara, M. Kurihara, and N. Yoda, *Tetrahedron* **25**, 783 (1969).

²²⁷ G. Doleschall and K. Lempert, *Tetrahedron* **25**, 2539 (1969).

²²⁸ T. L. Pilicheva, I. Ya. Postovskii, O. N. Chupakhin, N. A. Klyuev, and V. I. Chernyi, *Dokl. Akad. Nauk SSSR* **218**, 1375 (1974).

²²⁹ F. Claudi, P. Franchetti, M. Grifantini, and S. Martelli, *J. Org. Chem.* **39**, 3508 (1974).

²³⁰ R. D. Chambers, J. A. H. MacBride, and W. K. R. Musgrave, *Chem. Commun.*, 739 (1970).



one or 2-methylcinnol-3(2*H*)-one, was more efficient and gave 70–95% yields of the corresponding quinazolin-4-ones [Eq. (12)]. A zwitterionic diazabenzvalene (**101**) was also proposed as an intermediate in this transformation.²³¹

B. REARRANGEMENTS INVOLVING FIVE- AND SIX-MEMBERED RINGS

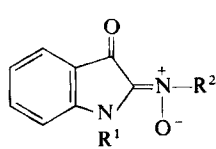
Several examples are known of the ring-expansion reactions that transform isatins into quinazolines. *N*-Carbamoyl isatins rearrange in the presence of amines into derivatives of 4-carboxy-4-hydroxy-3,4-dihydroquinazolin-2(1*H*)-ones,²³² and *N*-carbamoyl-3-(dicyano)methylene oxindoles provided 4-(dicyano)methylene-3,4-dihydroquinazolin-2(1*H*)-ones.²³³ The two isomeric *N*-oxides **102** and **103** underwent ring expansion on photolysis and produced the same 1,3-disubstituted quinazoline-2,4-diones (**104**) among other products, which include isatins. The ratio of products was sensitive

²³¹ D. E. Ames, S. Chandrasekhar, and R. Simpson, *J.C.S. Perkin I*, 2035 (1975).

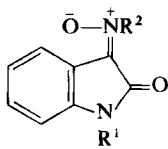
²³² S. Petersen, H. Heitzer, and L. Born, *Justus Liebigs Ann. Chem.*, 2003 (1974).

²³³ L. Capuano and V. Diehl, *Chem. Ber.* **109**, 723 (1976).

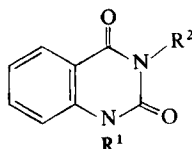
to the solvent used, and the evidence that oxaziridines were intermediates was borne out by their isolation in some examples.²³⁴



(102)



(103)



(104)

1-Alkylindazoles rearranged into 2-alkyl-1,2-dihydroquinazolines on treatment with butyl lithium or Grignard reagents. The respective 2-alkyl-1,2,3,4-tetrahydroquinazolines were obtained when the indazoles were reduced with lithium aluminum hydride.²³⁵ Hydrolysis of *trans*-4-*N'*-phenylureidoperhydroisoindol-1-one with 5*N*-hydrochloric acid gave the isomeric *cis*-8a-aminomethyl-3-phenyl-3,4,4a,5,6,7,8,8a-octahydroquinazolin-2(1*H*)-one, as would be expected from the known stability of a six-membered ring compared with a five-membered ring.²¹⁵

The reverse of the above transformation, i.e., conversion of a quinazoline into an indazole, has been observed. Thus photolysis of 6-chloro-2-methyl-4-phenylquinazoline 1-oxide provided 1-acetyl-5-chloro-3-phenylindazole, and most probably proceeded via 7-chloro-2-methyl-5-phenyl-3,1,4-benzoxadiazepine because the latter yields the same indazole on photolysis.²³⁶

C. TRANSFORMATIONS INVOLVING SIX- AND SEVEN- OR MORE MEMBERED RINGS

The main impetus that led to extensive studies of the conversion of quinazolines (e.g., **105**) into benzodiazepines (e.g., **106**), benzoxadiazepines, benzotriazocines (e.g., **108**) and benzoxadiazocines (e.g., **109**), and the reverse transformations, has been the wide medicinal usefulness of several benzodiazepines (e.g., Librium, Valium, Serax) as tranquilizers.²³⁷ The 2-chloro-methylquinazoline 3-oxide **105** reacted with alkylamines in which the alkyl group (e.g., methyl) is small to give the benzodiazepine oxide **106** ($R^1 = H$;

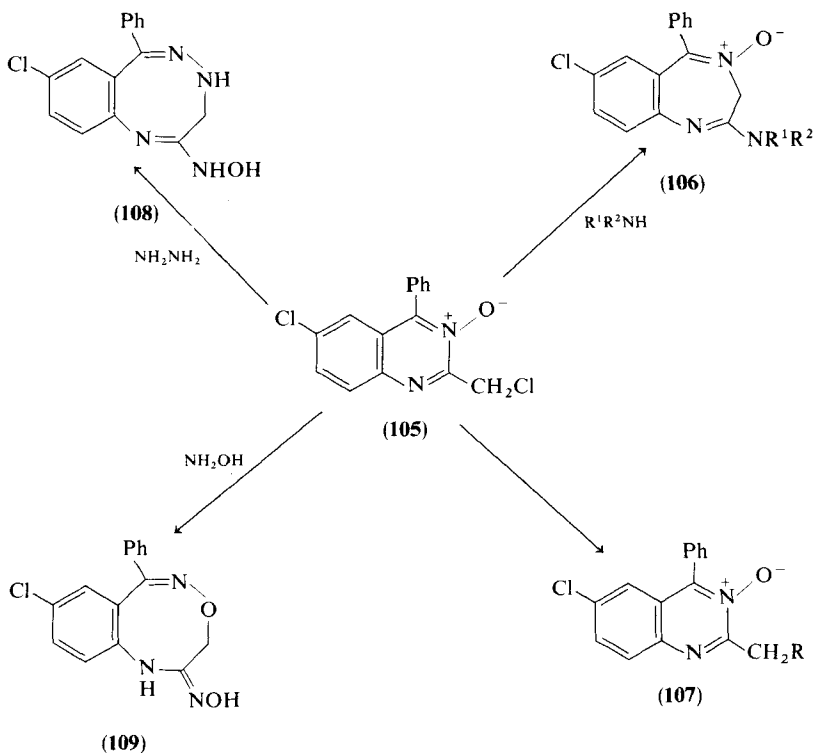
²³⁴ H. G. Aurich and U. Grigo, *Chem. Ber.* **109**, 200 (1976).

²³⁵ B. A. Tertov, P. P. Onishchenko, and V. U. Bessonov, *Khim. Geterotsikl. Soedin.*, 1410 (1974) [*CA* **82**, 140068 (1975)].

²³⁶ G. F. Field and L. H. Sternbach, *J. Org. Chem.* **33**, 4438 (1968).

²³⁷ S. Iacobescu-Cilianu, D. Beiu, M. Lazarescu, G. Neubauer, L. Ilie, and A. Ciuceanu, *Rev. Chim. Repub. Pop. Roum. Acad.* **25**, 869 (1974) [*CA* **82**, 125374 (1975)].

$R^2 = \text{Me}$; Librium). Dimethylamine, on the other hand, produced a mixture of the diazepine oxide (**106**: $R^1 = R^2 = \text{Me}$) together with the normal substitution product (**107**: $R = \text{NMe}_2$), and piperidine, cyclohexylamine, and mercaptans formed the normal products (**107**: $R = \text{piperidyl}$, $\text{NHC}_6\text{H}_{11}$, and SR^1). The polarizability of the nucleophile appeared to be more important than its steric properties.²³⁸ The reverse transformation was brought about by dilute aqueous acid, which in the presence of an aliphatic aldehyde converted **106** ($R^1 = \text{H}$; $R^2 = \text{Me}$) into the aldehyde adduct of 6-chloro-2-methylamino-4-phenylquinazoline 3-oxide.²³⁹ In the absence of an aldehyde, or with nitrous acid, **106** ($R^1 = \text{H}$; $R^2 = \text{Me}$) produced 6-chloro-4-hydroxy-2-hydroxyiminomethyl-3-methyl-4-phenyl-3,4-dihydroquinazoline.²⁴⁰ Simi-



SCHEME 2

²³⁸ H. S. Broadbent, R. C. Anderson, and M. C. J. Kuchar, *J. Heterocycl. Chem.* **14**, 289 (1977).

²³⁹ U. D. Shenoy, British Patent 1,413,600 (1975) [*CA* **84**, 90174 (1976)].

²⁴⁰ A. Walser, R. I. Fryer, L. H. Sternbach, and M. C. Archer, *J. Heterocycl. Chem.* **11**, 619 (1974).

larly 7-chloro-4,5-epoxy-5-phenyl-1,3,4,5-tetrahydro-2*H*-1,4-benzodiazepin-2-one was converted in good yield into 3-alkoxymethyl-6-chloro-4-hydroxy-4-phenyl-3,4-dihydroquinazolin-2(1*H*)-ones simply by boiling solutions of the epoxide in the respective alcohols.²⁴¹ Ring enlargement of 2-amino-methyl-6-chloro-4-hydroxy-3-methyl-4-phenyl-3,4-dihydroquinazoline to 6-chloro-2-methylamino-5-phenyl-3*H*-1,4-benzodiazepine (i.e., reduced **106**; $R^1 = H$; $R^2 = Me$) was achieved in acetic anhydride.²⁴⁰ 2-Carboxy-6-chloro-4-*o*-chlorophenylquinazoline was obtained by ring contraction from 7-chloro-5-*o*-chlorophenyl-2,3-dihydro-2-oxo-1*H*-1,4-benzodiazepin-3-ylphosphonic esters, by treatment with sodium hydride followed by oxidation and acidification with acetic acid.²⁴² Other similar ring contractions have been reported.²⁴³

4-Methyl-3,4-dihydro-5*H*-1,3,4-benzotriazepin-5-ones rearranged to 3-methylaminoquinazolin-4-ones under the influence of a base,²⁴⁴ but 3-methyl(or 4-methyl)-3,4-dihydro-5*H*-1,3,4-benzotriazepine-2,5-diones gave 3-methylquinazoline-2,4-diones in dimethylformamide containing sodium hydride and ethyl bromoacetate. Diaziridines were postulated as intermediates in the latter reactions.²⁴⁵ As in the rearrangement of 2,3-dihydro-5*H*-1,3,4-benzotriazepin-5-ones, 7-chloro-2-methylamino-5-phenyl-3*H*-3,1,4-benzoxadiazepine rearranged to 6-chloro-2-methylamino-4-phenylquinazoline 3-oxide in the presence of alkali.²²⁴

Hydrazine transformed the 3-oxide **105** into the benzotriazocine **108**, which was reduced to the corresponding 2-amino derivative with Raney nickel.²⁴⁶ The related 3*H*-4,1,5-benzoxadiazocine-2-one oxime **109** was obtained from **106** by treatment with hydroxylamine but, unlike **108**, ring-contraction occurred on reduction with Raney nickel, and 6-chloro-2-hydroxymethyl-4-phenylquinazoline was produced.²⁴⁷

Photolysis of 2-aryl-4-phenylquinazoline 3-oxides caused the oxygen atom to be inserted into the heterocyclic ring.^{236,248} The 3,4-epoxy intermediate must have undergone a 1,5-sigmatropic shift prior to electrocyclic ring opening to yield 2-aryl-4-phenyl-5,1,3-benzo oxadiazepines [Eq. (13)].²⁴⁸

²⁴¹ R. Y. Ning, I. Douvan, and L. H. Sternbach, *J. Org. Chem.* **35**, 2243 (1970).

²⁴² J. H. Sellstedt, *J. Org. Chem.* **40**, 1508 (1975).

²⁴³ R. I. Fryer, J. V. Earley, and J. F. Blount, *J. Org. Chem.* **42**, 2212 (1977).

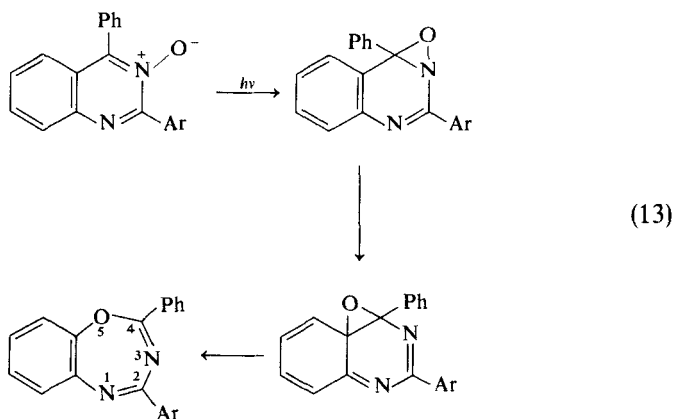
²⁴⁴ R. W. Leiby and N. D. Heindel, *J. Org. Chem.* **42**, 161 (1977).

²⁴⁵ S. Sunder and N. P. Peet, *J. Org. Chem.* **42**, 2551 (1977).

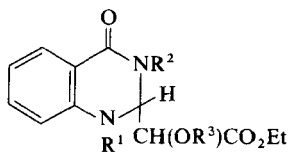
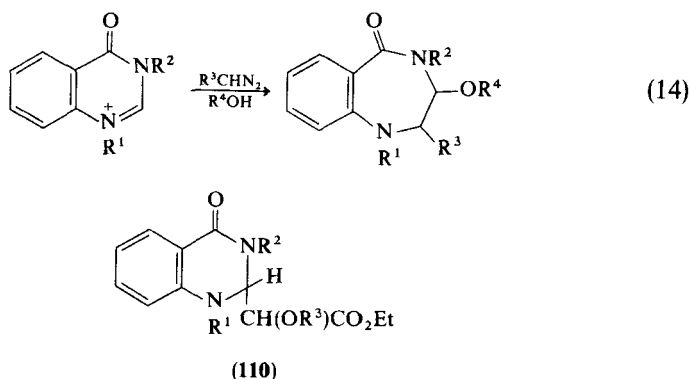
²⁴⁶ K. Meguor and Y. Kuwada, *Chem. Pharm. Bull.* **21**, 2375 (1973).

²⁴⁷ P. N. Giraldi, A. Fojanesi, G. P. Tosolini, E. Dradi, and W. Logemann, *J. Heterocycl. Chem.* **7**, 1429 (1970).

²⁴⁸ C. W. Rees, R. Somanathan, R. C. Storr, and A. D. Woolhouse, *J. Chem. Soc., Chem. Commun.*, 740 (1975).



A novel ring expansion of 1-alkyl-3-aryl-4-oxoquinazolinium salts was achieved, by the insertion of the α -carbon atom of diazoalkanes, in alcoholic solutions [Eq. (14)].²⁴⁹ Ethyl diazoacetate also added across the 1,2 double bond, but unlike simple diazoalkanes the adduct **110** did not rearrange.²⁵⁰



(110)

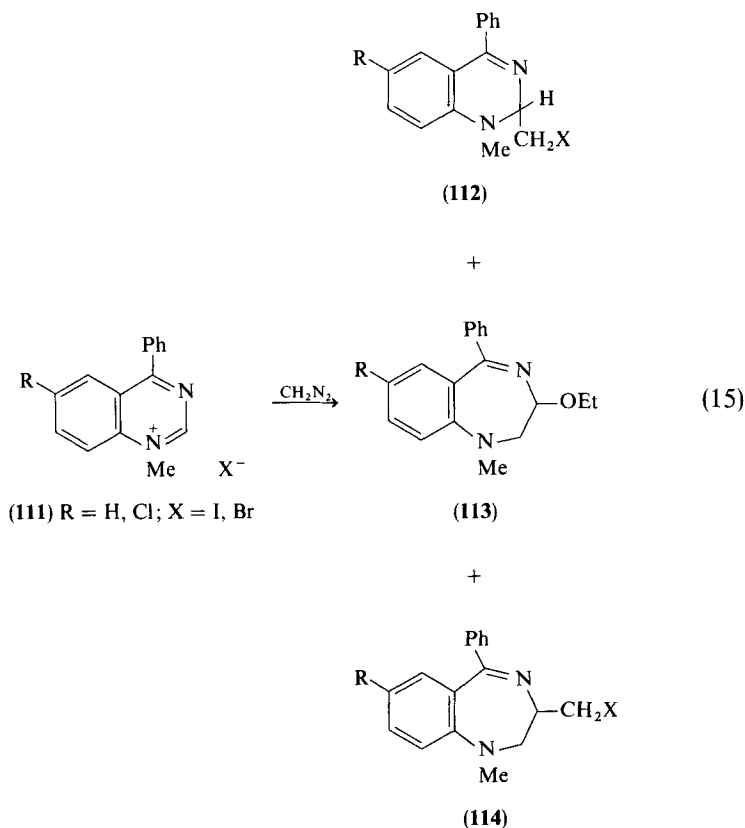
4-Aryl-1-methylquinazolinium salts (**111**) also reacted with diazomethane.²⁵¹ In this case, however, two molecules of diazoalkane could react with the quinazolinium salt. In anhydrous medium at 10°C the 1,2-dihydro adduct (**112**) was formed together with a 1:1 mixture (24% yield) of the benzo-diazepines **113** and **114**. At lower temperatures (-45°C), on the other hand, **114**, from reaction with two molecules of diazomethane, was the only product

²⁴⁹ I. Inoue, T. Ohine, and Y. Yamada, Japanese Patent 75 50,392 (1975) [*CA* **83**, 206339 (1975)].

²⁵⁰ Y. Yamada, T. Oine, and I. Inoue, *Bull. Chem. Soc. Jpn.* **47**, 339 (1974).

²⁵¹ T. Sugawara, Japanese Patent 75 112,388 (1975) [*CA* **84**, 59605 (1976)]; I. Inoue, T. Oine, and Y. Yamada, Japanese Patent 75 24,285 (1975) [*CA* **83**, 164252 (1975)].

obtained (55% yield).²⁵² This novel transformation of quinazolines into 1,4-benzodiazepines should be yet another means of preparing useful CNS-active drugs related to Librium and Valium (Section IX).



VIII. Naturally Occurring Quinazolines

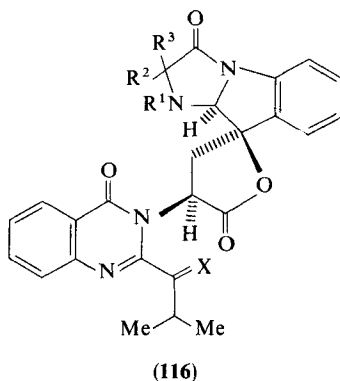
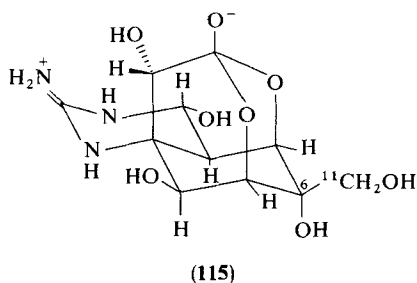
The chemistry of quinazoline alkaloids is being continuously updated in the specialist periodicals entitled "The Alkaloids" which are published by The Chemical Society (London).²⁵³ The sections on quinazoline alkaloids are thorough and should be consulted not only for information published prior to 1976, but also for future data in subsequent volumes. Other reviews

²⁵² Y. Yamada, T. Oine, and I. Inoue, *Bull. Chem. Soc. Jpn.* **47**, 343 (1974).

²⁵³ V. A. Snieckus, *Alkaloids* **2**, 91 (1972); **3**, 112 (1973); **4**, 124 (1974); **5**, 108 (1975); M. F. Grundon, *Alkaloids* **6**, 108 (1976).

dealing with quinazoline alkaloids have appeared.²⁵⁴ A few references on naturally occurring quinazolines that are not of plant origin are discussed in this section.

The total synthesis of *d,l*-tetrodotoxin (**115**, only the naturally occurring isomer shown) was accomplished by Kishi and his collaborators. The synthesis was very elegant, and consisted of several reactions which were developed particularly for this purpose, but which should be useful in other areas of organic chemistry. The pyrimidine ring was formed only in the final stages of the synthesis. Synthetic *d,l*-tetrodotoxin possessed half of the biological activity of the natural toxin.²⁵⁵ The hydroxymethyl side chain of the natural toxin was removed by oxidation, but the 11-*nor*-tetrodotoxin thus formed (the 6-OH and CH₂OH replaced by =O) was several hundredfold less active than the toxin. Some biological activity was regained, however, when a methoxyimino group was inserted at C-6 in 11-*nor*-tetrodotoxin.²⁵⁶ The synthesis of 11-succinylanhydrotetrodotoxin gave a derivative containing a functional group (carboxy), which could be used for attachment to an affinity column or to a large molecule.²⁵⁷ The latter application could be useful immunologically for discovering an antidote for the toxin. A tritiated tetrodotoxin was prepared,²⁵⁷ but attempts to incorporate radioactivity into the toxin from labeled acetate or arginine in *in vitro* experiments with ovaries of *Spheroides liosomus* have been unsuccessful so far.²⁵⁸ A few



²⁵⁴ D. Groeger, in "Biosynthesis der Alkaloide" (K. Mothes, ed.), p. 551. VEB Dsch. Verlag. Wiss., Berlin, 1961; S. Johné and D. Groeger, *Pharmazie* **25**, 22 (1970).

²⁵⁵ T. Kishi, T. Fukuyama, M. Aratani, F. Nakatsubo, T. Goto, S. Inoue, H. Tanino, S. Sugiura, and H. Kakoi, *J. Am. Chem. Soc.* **94**, 9219 (1972), and earlier papers.

²⁵⁶ R. Y. Tsien, D. P. L. Green, S. R. Levinson, B. Rudy, and J. K. M. Saunders, *Proc. R. Soc. London, Ser. B* **191**, 555 (1975).

²⁵⁷ P. N. Strong and J. F. W. Keana, *Bioorg. Chem.* **5**, 255 (1976).

²⁵⁸ W. L. F. Armarego and P. A. Reece, unpublished work, 1975.

studies directed at the synthesis of simple analogs of the toxin were reported (Sections VI,B and C), but the biological activities have been very low.²¹³

4-Methyl-, 2,4-dimethyl-, 2-ethyl-4-methyl-, 2-hydroxymethyl-4-methyl-, and 2-carbamoyl-4-methyl-quinazoline were isolated from *Pseudomonas aeruginosa*. (S)-Tryptophan was shown to be the precursor of these quinazolines by using the ¹⁴C-labeled amino acid in a new pathway of tryptophan biosynthesis⁷³ (see Section III,A).

Tremor-inducing mycotoxins were isolated from the mold *Aspergillus clavatus*, which infests rice. The mycotoxins were tetrapeptides of anthranilic acid (source of the quinazolin-4-ones), tryptophan, valine, and methyl-alanine or alanine. They were named tryptoquivaline (**116**: R¹ = OH, R² = R³ = Me; X = H, OAc) and nortryptoquivalone (**116**: R¹ = OH; R² = Me; R³ = H; X = O). The structures of the metabolites were deduced from spectral data, from the X-ray crystallographic analysis of the *p*-bromophenylurethan derivative of a transformation product of tryptoquivaline, and from chemical studies.²⁵⁹

IX. Biologically Active Quinazolines

A vast number of quinazolines have been synthesized for biological screening, and a variety of activities were observed. Several derivatives are being used clinically. Space does not permit a discussion of all the available literature, and only the various biological activities will be listed together with the respective structures. A few of the many references for each activity are provided, and *Chemical Abstracts* should be consulted for further references. Much of the data are in the Patent literature.

There was continuing interest in the effects of 3-arylquinazolin-4-ones on the central nervous system (CNS) which resulted from the known activity of methaqualone (**117**: Ar = *o*-tolyl; R¹ = Me; R² = H). A most extensive literature is available on the metabolism, pharmacology, and analytical chemistry of methaqualone. The effects of varying the group R¹ on CNS-depressant activity were reported.²⁶⁰ The structure **117** was associated with CNS-depressant²⁶¹ and tranquilizing^{262,263} activities, and 3- ω -aminoalkyl-

²⁵⁹ G. Büchi, K. C. Luk, B. Kobbe, and J. M. Townsend, *J. Org. Chem.* **42**, 244 (1977).

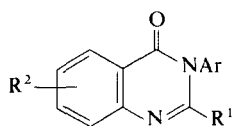
²⁶⁰ I. R. Ager, D. R. Harrison, P. D. Kennewell, and J. B. Taylor, *J. Med. Chem.* **20**, 379 (1977).

²⁶¹ V. K. Rastogi, R. C. Arora, J. N. Sinha, and S. S. Parmar, *J. Prakt. Chem.* **312**, 744 (1970).

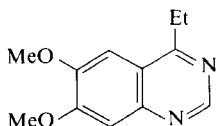
²⁶² Sumitomo Chem. Co., French Patent 1,572,997 (1969) [*CA* **72**, 90495 (1970)].

²⁶³ F. Kusuda, M. Murayama, and H. Takahashi, Japanese Patent 71 18,996 (1971) [*CA* **75**, 49128 (1971)]; Japanese Patent 71 18,995 (1971) [*CA* **75**, 63823 (1971)].

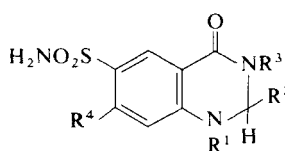
1,2-dihydro-²⁶⁴ and 2,3-polymethylene-quinazolin-4-ones²⁶⁵ also possessed activity toward the CNS. 4-Substituted aminoquinazolines (antidepressants and stimulants)²⁶⁶ and 4,4-dimethyl-3,4-dihydroquinazolin-2(1*H*)-ones (anticonvulsants)²⁶⁷ had CNS activity. 3-*o*-Aminoalkyl-²⁶⁸ and 2-substituted quinazolin-4-ones^{269,270} and thiones,²⁷¹ 2,4-diaminoquinazolines,^{272,273} 3-ethoxycarbonylmethyl-3,4-dihydroquinazolin-2(1*H*)-ones,²⁷⁴ and 2,3-dihydroimidazo[1,2-*c*]quinazolines²⁷⁵ possessed hypotensive activity.



(117)



(118)



(119)

The analgesic (5-ethoxy-2-dimethylaminomethyl-3-methylquinazolin-4-one²⁷⁶ and 4,2'-thienylquinazolines²⁷⁷), antithrombic and anticoagulant (2-vinyl-1,4-dihydroquinazolines),²⁷⁸ and antifibrillatory (1-aminoacyl-1,2-dihydroquinazolin-4-ones)²⁷⁹ action of quinazoline derivatives were patented, and 2-phenoxy-carbonyloxymethyl-3-substituted-quinazolin-4-ones were potentially useful drugs for the treatment of arteriosclerosis.²⁸⁰ The effects of Quinazodine (**118**) as a cardiac stimulant and its hemodynamic

²⁶⁴ E. S. Schipper, U.S. Patent 3,322,766 (1967) [CA 67, 64424 (1967)]; U.S. Patent 3,316,269 (1967) [CA 67, 64433 (1967)].

²⁶⁵ G. Devi, R. S. Kapil, and S. P. Popli, *Indian J. Chem.* **14B**, 354 (1976).

²⁶⁶ G. E. Hardtmann and H. Ott, U.S. Patent 3,470,182 (1969) [CA 72, 90502 (1970)].

²⁶⁷ L. Bernardi, A. Bonsignori, S. Coda, and G. K. Suchowsky, German Patent 1,958,515 (1970) [CA 73, 77279 (1970)].

²⁶⁸ S. Hayao, H. J. Havera, W. G. Strycker, and E. Hong, *J. Med. Chem.* **12**, 936 (1969).

²⁶⁹ Chas. Pfizer and Co., British Patent 1,062,357 (1967) [CA 68, 29720 (1968)].

²⁷⁰ Chas. Pfizer and Co., British Patent 1,174,272 (1969) [CA 72, 90496 (1970)].

²⁷¹ Chas. Pfizer and Co., British Patent 1,174,273 (1969) [CA 72, 90497 (1970)].

²⁷² Chas. Pfizer and Co., British Patent 1,156,973 (1969) [CA 71, 91519 (1969)].

²⁷³ H. J. E. Hess, Japanese Patent 76 80,877 (1976) [CA 86, 89891 (1977)].

²⁷⁴ W. N. Beverung and R. A. Partyka, U.S. Patent 3,983,120 (1976) [CA 86, 72688 (1977)].

²⁷⁵ G. E. Hardtmann and H. Ott, German Patent 1,946,188 (1970) [CA 72, 132774 (1970)].

²⁷⁶ Farbwerke Hoechst A.-G., French Patent 3,806 (1966) [CA 71, 91518 (1969)].

²⁷⁷ H. Ott, Swiss Patent 491,134 (1970) [CA 73, 120668 (1970)].

²⁷⁸ D. A. Cox, German Patent 1,918,154 (1969) [CA 72, 79086 (1970)].

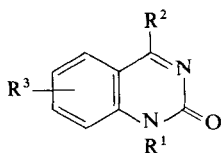
²⁷⁹ G. Bonola, P. DaRe, and I. Setnikar, Swiss Patent 474,524 (1969) [CA 72, 3500 (1970)]; Swiss Patent 474,525 (1967) [CA 72, 3501 (1970)].

²⁸⁰ M. Inoue, M. Ishikawa, T. Tsuchiya, and T. Shimamoto, Japanese Patent 73 22,481 (1973) [CA 79, 42544 (1973)].

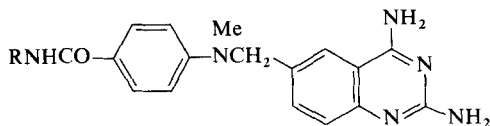
properties were studied.^{281,282} Quinazodine and its 3-oxide were also tested for bronchodilatory activity.²⁸³

Many more 1,2-dihydroquinazolin-4-ones with the general structure **119** were tested for diuretic activity in attempts to improve on the activity of "Quinethazone."²⁸⁴

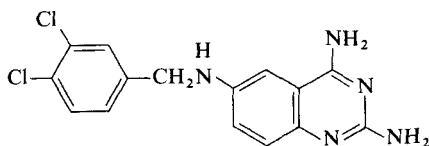
A large number of quinazolin-2-ones with the general structure **120** were examined for anti-inflammatory activity,²⁸⁵⁻²⁸⁹ and quinazoline-1,3-



(120)



(121) R = Asp or Glu



(122)

²⁸¹ J. R. Parratt and E. Winslow, *Clin. Exp. Pharmacol. Physiol.* **1**, 31 (1974) [*CA* **81**, 163368 (1974)].

²⁸² A. W. Gomoll, J. E. Byrne, and G. R. McKinney, *Arch. Int. Pharmacodyn. Ther.* **207**, 16 (1974).

²⁸³ S. Umio, K. Kariyone, H. Zenno, and T. Kamiya, Japanese Patent 12,670 (1967) [*CA* **68**, 21951 (1968)].

²⁸⁴ B. V. Shetty, U.S. Patent 3,549,634 (1970) [*CA* **75**, 5940 (1971)]; U.S. Patent 3,549,636 (1970) [*CA* **75**, 5933 (1971)]; U.S. Patent 3,557,117 (1971) [*CA* **75**, 5928 (1971)]; U.S. Patent 3,539,570 (1970) [*CA* **74**, 42378 (1971)]; U.S. Patent 3,549,637 (1970) [*CA* **75**, 5942 (1971)].

²⁸⁵ E. Wulfert, P. Bolla, and J. Mathieu, *Chim. Ther.* **4**, 257 (1969) [*CA* **72**, 35763 (1970)].

²⁸⁶ H. Ott, South African Patent 68 03,396 (1969) [*CA* **73**, 45541 (1970)].

²⁸⁷ H. Ott and W. J. Houlihan, Swiss Patent 499,544 (1971) [*CA* **75**, 20435 (1971)].

²⁸⁸ G. E. Hardtmann, U.S. Patent 3,563,990 (1971) [*CA* **75**, 5930 (1971)].

²⁸⁹ M. Kimura, T. Hirohashi, and H. Yamamoto, *Bull. Chem. Soc. Jpn.* **49**, 2696 (1976); S. Inaba, M. Yamamoto, K. Takahashi, K. Mori, K. Ishizumi, and H. Yamamoto, German Patent 1,935,404 (1970) [*CA* **72**, 90494 (1970)].

dioxides¹⁷⁷ and 3-aryl-1,2-dihydroquinazolin-4-ones¹⁷⁷ showed some activity. A drug to relieve arthritis may well come out of this work.

Quinazolines have been prepared with the aim of discovering useful drugs for cancer chemotherapy. All the studies were directed toward synthesizing quinazolines that had some resemblance to folic acid.²⁹⁰⁻²⁹⁷ These compounds were tested for inhibition of the enzyme dihydrofolate reductase. The analogs **121** were even slightly more potent than methotrexate as inhibitors of dihydrofolate reductase in human leukemia cells.^{298,299} Simpler analogs (e.g., **122**) were similarly found to be as active as methotrexate toward dihydrofolate reductase from rat liver and L1210 mouse leukemia.³⁰⁰ 1-³⁰¹ and 3-substituted quinazolin-4-ones,^{302,303} and 2-substituted-4-(substituted-amino)quinazolines,^{303,304} possessed biocidal activity, and efforts are still being made to obtain satisfactory antimalarial activity in quinazoline derivatives.^{305,306}

Quinazoline-2,4-diones,³⁰⁷ octahydroquinazoline-2,4-diones (herbicides),³⁰⁸ and 3-*O*-carbonate esters of quinazolin-4-ones (fungicides)³⁰⁹ were tested for agricultural purposes, and 2-phenyl-1,2-dihydroquinazolin-4(3*H*)-one had insecticidal activity with a possible use for controlling the

²⁹⁰ J. B. Hynes, J. M. Buck, L. D'Souza, and J. H. Freisheim, *J. Med. Chem.* **18**, 1191 (1975).

²⁹¹ J. Y. Fukunaga, C. Hansch, and E. E. Steller, *J. Med. Chem.* **19**, 605 (1976).

²⁹² J. B. Hynes, D. E. Eason, C. M. Garrett, P. L. Colvin, K. E. Shores, and J. H. Freisheim, *J. Med. Chem.* **20**, 588 (1977).

²⁹³ A. Rosowsky, J. L. Marini, M. E. Nadel, and E. J. Modest, *J. Med. Chem.* **13**, 882 (1970).

²⁹⁴ A. M. Albrecht, D. J. Hutchinson, F. K. Pearce, and W. J. Suling, *Mol. Pharmacol.* **6**, 323 (1970).

²⁹⁵ F. I. Carroll, B. Berrang, and C. P. Linn, *Chem. Ind. (London)*, 477 (1975).

²⁹⁶ J. Davoll, British Patent 1,135,898 (1968) [*CA* **70**, 47487 (1969)].

²⁹⁷ J. Davoll and A. M. Johnson, *J. Chem. Soc. C*, 997 (1970).

²⁹⁸ D. G. Johns, R. L. Capizzi, A. Nahas, A. R. Cashmore, and J. R. Bertino, *Biochem. Pharmacol.* **19**, 1528 (1970).

²⁹⁹ D. J. Hutchison, *Cancer Chemother. Rep.* **52**, 697 (1968).

³⁰⁰ W. E. Richter and J. J. McCormack, *J. Med. Chem.* **17**, 943 (1974).

³⁰¹ K. Issleib, H. P. Abicht, H. Oehme, and W. Kochmann, East German Patent 91,823 (1972) [*CA* **78**, 43507 (1973)].

³⁰² K. M. Murav'eva, N. V. Arkhangel'skaya, M. N. Shchukina, T. N. Zykova, and G. N. Pershin, *Khim.-Farm. Zh.* **2**, 35 (1968) [*CA* **69**, 106658 (1968)].

³⁰³ E. F. Harrison and A. A. Larsen, U.S. Patent 3,560,619 (1971) [*CA* **75**, 5929 (1971)].

³⁰⁴ R. J. Alaimo, U.S. Patent 3,997,538 (1976) [*CA* **86**, 121366 (1977)].

³⁰⁵ P. N. Bhargava and M. R. Chaurasia, *J. Med. Chem.* **11**, 908 (1968).

³⁰⁶ P. A. Cruickshank and W. E. Hymans, *J. Med. Chem.* **17**, 468 (1974).

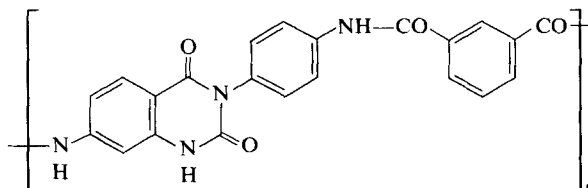
³⁰⁷ R. H. Fish, British Patent 1,139,627 (1969) [*CA* **70**, 68420 (1969)].

³⁰⁸ A. Zeidler, A. Fischer, F. Reicheneder, and W. Himmele, South African Patent 68 08,579 (1969) [*CA* **72**, 79084 (1970)].

³⁰⁹ Fisons Ltd., French Patent 1,520,873 (1968) [*CA* **71**, 13141 (1969)].

house fly.³¹⁰ 2-Alkoxycarbonylamino-3,4-dihydroquinazolines possessed some anthelmintic activity.³¹¹

Various biological activities were found in the following derivatives: 2,4-bis(dialkylaminoalkyl)quinazolines (curare mimetics),³¹² 1-(ω -dimethylaminoalkyl)-3-substituted quinazoline-2,4-diones (inhibition of gastric secretions),³¹³ 4-alkoxycarbonylmethylthioquinazolines (radioactivity protecting agents),³¹⁴ and 2-amino-6-hydroxymethyl(or formyl)quinazolin-4-ones (xanthine oxidase inhibitors).³¹⁵



(123)

X. Industrial Uses

Some biologically active quinazolines described in the preceding section were used in the manufacture of drugs, and several biologically inactive derivatives have also been used in industry. The quinazoline nucleus is synthesized readily and cheaply on the industrial scale and, depending on substitution, the heterocyclic or aromatic carbocyclic portion of the molecule can be used for further reactions. Azo compounds based on quinazolin-4-ones were used for dyeing,^{316,317} and pigments were made by condensing two 2-methylquinazolin-4(3*H*)-one molecules with one of pyromellitic anhydride.³¹⁸ Polyquinazolinodione polymers,³¹⁹ and polymers

³¹⁰ B. Stearns, German Patent 1,927,691 (1969) [CA 72, 54085 (1970)].

³¹¹ G. L. Dunn, U.S. Patent 3,535,321 (1970) [CA 74, 42377 (1971)].

³¹² R. E. Orth, *J. Pharm. Sci.* **56**, 925 (1967).

³¹³ B. Danielsson and L. Kornberg, *Acta Pharm. Suec.* **6**, 389 (1969).

³¹⁴ J. Tulecki and J. Kalinowska-Torz, *Ann. Pharm. (Poznan)* **7**, 17 (1969) [CA 72, 55402 (1970)].

³¹⁵ D. G. Priest, J. B. Hynes, C. W. Jones, and W. T. Ashton, *J. Pharm. Sci.* **63**, 1158 (1974).

³¹⁶ H. Junge and W. Kurtz, German Patent 2,507,908 (1976) [CA 85, 161874 (1976)].

³¹⁷ A. Arcoria and G. Scarlata, *Gazz. Chim. Ital.* **96**, 279 (1966).

³¹⁸ K. Shibata, Japanese Patent 73 93,622 (1973) [CA 81, 122785 (1974)].

³¹⁹ E. I. Khofbauer, B. R. Lifshits, M. B. Fromberg, T. Kh. Dymshits, G. I. Vainshtein, and V. G. Kolesnikov, USSR Patent 407,932 (1973) [CA 82, 17464 (1975)].

derived from repeating units such as **123**, gave useful fibers.³²⁰ 2-(*o*-Hydroxyphenyl)quinazolines have been patented as absorbers of UV light.³²¹

Note Added in Proof

Quinazoline readily forms 3,4-adducts in non-polar, neutral or moderately basic media (see Section IV,C). In aqueous acid the 3,4-hydrated cation is produced (Eq. 4), and in the presence of neutral aromatic nucleophiles in inert solvents (benzene, CS₂, CH₂Cl₂) containing non-aqueous proton acids, e.g. formic acid, a variety of 3,4-adducts can be obtained. 9-Methylanthracene, benzo[*a*] (and [*b*]) pyrene, perylene, resorcinol, thiophene, and indole react with quinazoline in benzene containing excess of trifluoroacetic acid to give high yields of the respective adducts, e.g. 4-(2',4'-dihydroxyphenyl)-3,4-dihydroquinazolinium trifluoroacetate from resorcinol. By comparison, quinazoline cation is a more reactive electrophile in these additions than are pyrimidines and purines.³²² Girke studied these reactions in some detail using quinazoline or 2-methylquinazoline and a variety of nucleophiles, e.g. phenols, anisole, naphthalene, anthracene, and indole. The 3,4-adducts were obtained in 70–100% yields when the additions were carried out at room temperature, or short reflux periods, in benzene containing trifluoroacetic acid, in acetic acid or formic acid, or by using quinazoline hydrochloride in methanol.³²³ Higashino, Kawada, and Hayashi found that such additions can be performed in 2N-aqueous sulfuric acid at room temperature, but the yields were higher with aromatic nucleophiles than with phenols. Thus 4-(*p*-aminophenyl)- and 4-(*p*-hydroxyphenyl)-3,4-dihydroquinazolines were formed in 100 and 35% yields, respectively.³²⁴

N-(6,7-Methylenedioxy-3-quinazolinio)amidates (**125**) are zwitterions formed by the cyclization of the *N*'-acylhydrazones of *o*-amidophenyl ketones (**124**) with thionyl or phosphoryl chloride followed by basification. They readily dimerize and form the adducts (**127**) by attack of nucleophiles at C-4. These adducts are in equilibrium with the zwitterions **125** and their dimers **126**. The relative proportions of these quinazolines depend on the solvent, temperature, and the substituents R¹, R², R³, and R⁴.³²⁵ The

³²⁰ G. D. Wolf, R. Miessen, H. E. Kuenzel, and F. Bentz, German Patent 2,438,546 (1976) [CA **84**, 152122 (1976)]; German Patent 2,438,545 (1976) [CA **84**, 152123 (1976)].

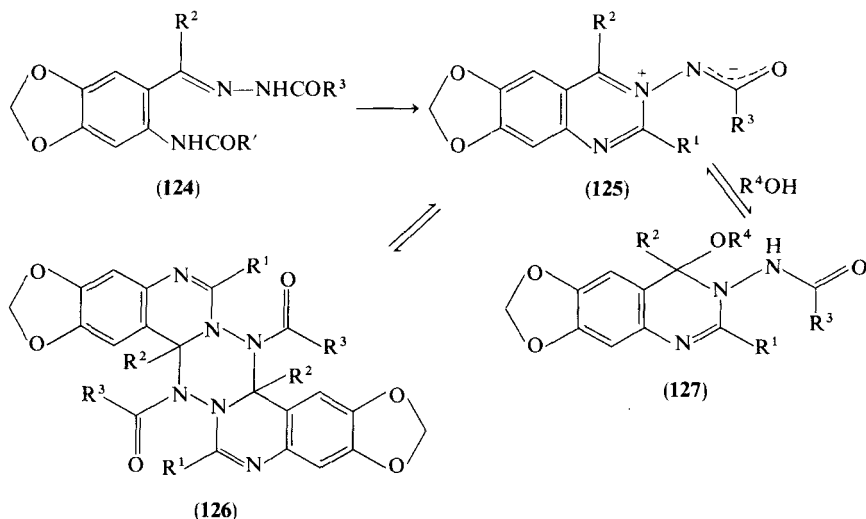
³²¹ J. E. A. Otterstedt and R. Pater, German Patent 1,935,382 (1970) [CA **72**, 90511 (1970)].

³²² W. Girke, *Tetrahedron Lett.*, 3537 (1976).

³²³ W. Girke, personal communication, 1978.

³²⁴ T. Higashino, Y. Kawada, and E. Hayashi, *Heterocycles* **8**, 159 (1977).

³²⁵ J. Fetter, K. Lempert, and K. Möller, *Tetrahedron* **31**, 2559 (1975).



related 6-methyl- and 6-phenyl- 9,10-dimethoxy-2*H*-[1,2,4]thiadiazino-[3,2-*c*]quinazolin-5-ium-3-olates were also described, but these cannot dimerize in the same way.³²⁶ When several *N*-(3-quinazolinio)amidates (125, R¹, R² = H, Me, R³ = OEt, OCH₂Ph, Ph) were photolyzed in ethanol and benzyl alcohol, six types of heterocyclic transformation products were isolated and characterized. These were 4-acyl-5-alkoxy-4,5-dihydro-3*H*-1,3,4-benzotriazepines, 2,4-dialkylquinazolines, 1,2-di(4-quinazolinyl)ethanes, *N*-(4-quinazolinylmethyl)carbamates, 4-alkoxyquinazolines, and 3-acylaminoquinazolin-4-ones. The relative amounts of these products depended on the nature of the substituents and whether or not oxygen was present during photolysis. The structure of one of these products, 4-benzoyl-5-ethoxy-2-methyl-4,5-dihydro-3*H*-1,3,4-benzotriazepine, was confirmed by an X-ray analysis.³²⁷

³²⁶ M. Lempert-Stréter, K. Lempert, P. Bruck, and G. Tóth, *Acta Chim. Acad. Sci. Hung.* **94**, 391 (1977).

³²⁷ J. Fetter, K. Lempert, G. Barta-Szalai, J. Møller, and L. Parkanyi, *Acta Chim. Acad. Sci. Hung.* **94**, 233 (1977).

Three-Membered Rings with Two Heteroatoms

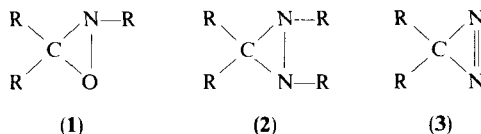
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I. Introduction

The present review is concerned with the chemistry of oxaziridines (1), diaziridines (2), and diazirines (3), three classes of compounds discovered after 1950 and widely investigated since then.



A short review appeared in this series in 1963,¹ followed in 1967 by a monograph recording the complete information on the field up to 1966. It

¹ E. Schmitz, *Adv. Heterocycl. Chem.* **2**, 83 (1963).

was first published in German,² and later, with some additions, in Russian (1970).³

This chapter follows the German version of this monograph, recording progress in the field from the middle of 1966 up to the middle of 1976. Reference is made to earlier work only when relevant to that published later. This review deals preferentially with synthesis, transformation, and decomposition of three-membered rings. With regard to the scope of this chapter, most spectroscopic data have not been included, especially those obtained from studies on general spectroscopic questions, which reached far beyond the field of heterocyclic compounds. Not included for the same reason are quantum chemical investigations carried out with diazirines, the cyclic isomers of aliphatic diazo compounds; they have been the subject of a recent review.⁴

It was the author's concern to use, but not to record, all published information in the field. For further information, see references 5–9.

II. Oxaziridines

A. SYNTHESIS OF 2-ALKYLOXAZIRIDINES

The synthesis of oxaziridines from Schiff bases and peracids, as reported by Krimm,¹⁰ Emmons,¹¹ and Horner and Jürgens,¹² is still the most popular procedure for their preparation [Eq. (1)].

² E. Schmitz, "Dreiringe mit zwei Heteroatomen, Oxaziridine, Diaziridine, cyclische Diazoverbindungen." Springer-Verlag, Berlin and New York, 1967.

³ E. Schmitz, "Trečtschlennye Zikly s Dvumja Geteroatomami." MIR, Moscow, 1970.

⁴ W. A. Lathan, L. Radom, P. C. Hariharan, W. J. Hehre, and J. A. Pople, *Top. Curr. Chem.* **40**, (1973).

⁵ Oxaziridines (a) W. D. Emmons, *Chem. Heterocycl. Comp.* **19** (1), 624 (1964); (b) J.-F. Dupin, *Bull. Soc. Chim. Fr.*, 3085 (1967); (c) W. Rundel, in "Methoden der Organischen Chemie" (J. Houben, Th. Weyl, and E. Müller, eds.), Vol. X, Part 4, pp. 449–472. Thieme, Stuttgart, 1968; (d) G. G. Spence, E. C. Taylor, and O. Buchardt, *Chem. Rev.* 236 (1970).

⁶ Photochemistry of Three-membered Ring Heterocycles: N. R. Bertonnière and G. W. Griffin, *Org. Photochem.* 105 (1973).

⁷ Diaziridines and Oxaziridines: D. J. Matland, *Saturated Heterocycl. Chem. (Chem. Soc., Spec. Period. Rep.)* **3**, 1–91 (1975).

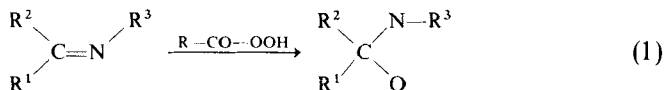
⁸ Diaziridines: E. Müller, in "Methoden der Organischen Chemie" (J. Houben, Th. Weyl, and E. Müller, eds.), Vol. X, Part 2, pp. 71–84. Thieme, Stuttgart, 1967.

⁹ Diaziridines and Diazirines: R. A. Reed, *Chem. Ind. (London)*, 529 (1966); Diazirines: M. Bauer and E. Müller, in "Methoden der Organischen Chemie" (J. Houben, Th. Weyl, and E. Müller, eds.), Vol. X, Part 4, pp. 895–922. Thieme, Stuttgart, 1968.

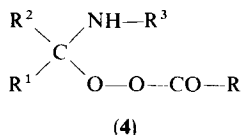
¹⁰ H. Krimm (Farbenfabriken Bayer, A.G.), British Patent 743, 940 (1953); C, 265 (1957).

¹¹ W. D. Emmons, *J. Am. Chem. Soc.* **78**, 6208 (1956); **79**, 5739 (1957).

¹² L. Horner and E. Jürgens, *Chem. Ber.* **90**, 2184 (1957).

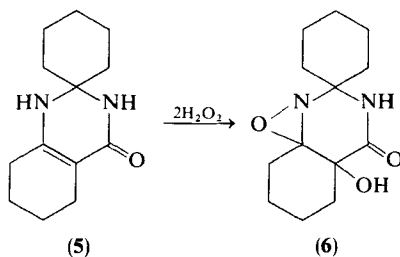


Kinetic investigations failed to distinguish between a one-step reaction of the olefin epoxidation type¹³ and a two-step reaction through an adduct such as **4**.¹⁴ The formation of Z,E isomeric mixtures of oxaziridines from sterically definite Schiff bases¹⁵ supports the two-step mechanism.



Application of new oxidizing reagents has led to new procedures of oxaziridine synthesis. Alkyl hydroperoxides in the presence of catalytic amounts of molybdenum compounds, the reagent of Halcon epoxidation, makes oxaziridines from Schiff bases in good yield.¹⁶ Further reagents successfully applied include the adduct of hydrogen peroxide to benzoyl isocyanate ($\text{Ph}-\text{CO}-\text{NH}-\text{CO}-\text{OOH}$),¹⁷ mixtures of hydrogen peroxide with nitriles,¹⁸ which are assumed to contain the peracid analog $\text{RC}(\text{NH})\text{OOH}$, $\text{SeO}_2 + \text{H}_2\text{O}_2$,¹⁹ as well as the hydroperoxides F_3COOH and F_5SOOH .²⁰

In certain cases, hydrogen peroxide alone is sufficient to prepare oxaziridines. The hydroxyoxaziridine **6** was obtained (70% yield) from **5** with hydrogen peroxide in dilute sulfuric acid at 60°C.²¹



¹³ Y. Ogata and Y. Sawaki, *J. Am. Chem. Soc.* **95**, 4687, 4692 (1973).

¹⁴ V. Madan and L. B. Clapp, *J. Am. Chem. Soc.* **91**, 6078 (1969); **92**, 4902 (1970).

¹⁵ D. R. Boyd, W. B. Jennings, R. Spratt, and D. M. Jerina, *Chem. Commun.*, 745 (1970).

¹⁶ G. A. Tolstikov, U. M. Emileev, V. P. Yur'ev, F. B. Gershanov, and S. R. Rafikov, *Tetrahedron Lett.*, 2807 (1971).

¹⁷ E. Hoeft and S. Ganschow, *J. Prakt. Chem.* **314**, 145 (1972).

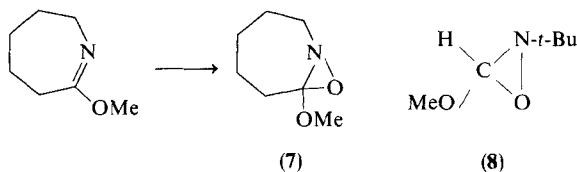
¹⁸ J. P. Schirrmann and F. Weiss, *Tetrahedron Lett.*, 633 (1972).

¹⁹ P. Tellier and F. Weiss, German Patent 2,351,079 (1974) [*CA* **81**, 91503 (1974)].

²⁰ E. R. Falardeau and D. D. DesMarteau, *J. Am. Chem. Soc.* **98**, 3529 (1976).

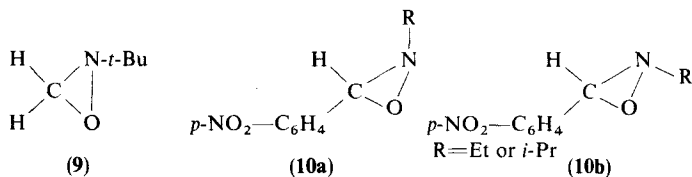
²¹ C. Bischoff, *J. Prakt. Chem.* **318**, 848 (1976).

There are apparently no limitations in the structure of the Schiff base. Oxaziridines were prepared from cyclic azomethines in the steroid field;²² Schiff bases with benzazepine structures were converted into oxaziridines, first by Metlesics and Sternbach,²³ later by other groups.^{24,25} The preparation of oxaziridines from imino ethers has been described in recent papers,^{26,27} e.g., the preparation of **7** and **8**.



B. CONFIGURATIONAL STABILITY AT THE OXAZIRIDINE NITROGEN

A series of papers deal with the remarkable stability of configuration at nitrogen of the oxaziridines. As early as 1957 Emmons¹¹ had observed splitting of the nuclear magnetic resonance (NMR) signals of the ring protons of the oxaziridine **9** and had discussed their spatial arrangement *cis* and *trans* to the *N*-alkyl together with the question of configurational stability. The existence of *E-Z* isomeric oxaziridines was discussed by Mannschreck *et al.*²⁸ and by Brois²⁹ on the basis of a detailed NMR investigation.



Configurational stability became evident from the preparative results, when both diastereomeric oxaziridines with *E-Z* isomerism and optically active oxaziridines were prepared.

²² X. Lusinchi, *Tetrahedron Lett.*, 177 (1967).

²³ W. Metlesics and L. H. Sternbach, U.S. Patent 3,498,973 (1970) [*CA* **72**, 132811 (1970)].

²⁴ B. J. Hester, U.S. Patent 3,681,343 (1972) [*CA* **77**, 126707 (1972)].

²⁵ O. Hromatka, M. Knollmüller, and D. Binder, *Monatsh. Chem.* **99**, 1117 (1968).

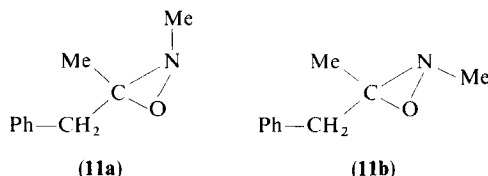
²⁶ D. St. C. Black, R. F. C. Brown, and A. M. Wade, *Tetrahedron Lett.*, 4519 (1971).

²⁷ D. Thomas and D. H. Aue, *Tetrahedron Lett.*, 1807 (1973).

²⁸ A. Mannschreck, R. Radeaglia, E. Gründemann, and R. Ohme, *Chem. Ber.* **100**, 1728 (1967).

²⁹ S. J. Brois, *J. Am. Chem. Soc.* **90**, 506 (1968).

Boyd separated crystalline isomers **10a** and **10b**.³⁰ As predicted from the NMR measurements, isomerization of a Z isomer to the E compound required 16 hours at 130°C.³¹ A similar separation of the 3-benzyl-2,3-dimethyloxaziridines **11** was carried out by Mannschreck.³²



The structural assessment was made by comparison of NMR data with those of E,Z-isomeric diaziridines. Oxaziridines **11a** and **11b** formed an equilibrium ratio 79:21; it is plausible that the methyl group prefers the less crowded side of the ring. Equilibrium could be reached from either pure **11a** or pure **11b**; free enthalpies of activation were 32.4 and 31.4 kcal mol⁻¹, respectively.

Later N-aryloxaziridines were separated into E and Z isomers and the barriers of interconversion were determined. It amounted to 23.2 kcal in the case of 3-methyl-2,3-diphenyloxaziridine.³³

Optically active oxaziridines with the optical activity due only to the hindered inversion at nitrogen were prepared by Montanari *et al.*³⁴ and by Boyd and Graham.³⁵ Schiff bases of benzophenone and of cyclohexanone were allowed to react with optically active peracids. Since the starting carbonyl compounds were symmetrically substituted, the oxaziridine nitrogen was the only center of asymmetry, and the barrier to inversion at nitrogen was the only cause of optical activity.

The enthalpies of activation of racemization amounted to 34.1 kcal mol⁻¹ in the case of 2-methyl-3,3-diphenyloxaziridine, but only to 27.7 kcal mol⁻¹ in the case of the N-*t*-butyl compound;³⁶ the entropies of activation were +5 and +6 cal mol⁻¹ deg⁻¹, respectively. Further investigations into the dependence of racemization on N- and C-substituents of the oxaziridine ring were carried out by Bjorgo and Boyd.³⁷

³⁰ D. R. Boyd, *Tetrahedron Lett.*, 4561 (1968).

³¹ Boyd *et al.*¹⁵; see also D. R. Boyd, R. Spratt, and D. M. Jerina, *J. Chem. Soc. C*, 2650 (1969).

³² A. Mannschreck, J. Linsz, and W. Seitz, *Justus Liebigs Ann. Chem.* **727**, 224 (1969).

³³ H. Ono, J. S. Splitter, and M. Calvin, *Tetrahedron Lett.*, 4107 (1973).

³⁴ F. Montanari, I. Moretti, and G. Torre, *Chem. Commun.*, 1694 (1968).

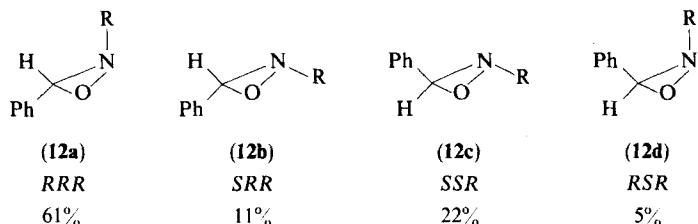
³⁵ D. R. Boyd and R. Graham, *J. Chem. Soc. C*, 2648 (1969).

³⁶ F. Montanari, I. Moretti, and G. Torre, *Chem. Commun.*, 1086 (1969).

³⁷ J. Bjorgo and D. R. Boyd, *J.C.S. Perkin II*, 1575 (1973).

Asymmetry of the oxaziridine nitrogen may be induced by means of an optically inactive peracid, when the Schiff base of an optically active amine is used.^{38,39} Starting with the Schiff base of benzophenone and *R*- α -phenylethylamine, preferentially *S*-configured oxaziridine nitrogen was produced.³⁸

The asymmetric synthesis of optically active oxaziridines was carefully investigated by Belzecki and co-workers.^{40,41} Starting with *E*-benzylidene-*R*- α -phenylethylamine, they obtained with *m*-chloroperbenzoic acid the four isomers **12a-d**, in the yields indicated.



The *E*-relation of phenyl and alkyl is retained to the extent of 83% (**12a** and **12c**); the yield differences **12a** versus **12c** and **12b** versus **12d** indicate a remarkable degree of asymmetric induction.

The absolute configuration of an oxaziridine made from *p*-bromobenzylidene- α -*S*-phenylethylamine has been determined by X-ray analysis.⁴¹

To explain the high barrier of inversion, all investigators refer to the strain of a three-membered ring with a substituent in the plane of a ring, required as the transition state of inversion. In addition, the stability of the tetrahedral arrangement in *N*-chloroaziridines and in hydroxylamine derivatives shows that heteroatoms directly linked to the nitrogen atom increase the barrier to equilibration.

C. REACTIONS OF 2-ALKYLOXAZIRIDINES

Simple reactions of oxaziridines, such as their behavior toward acids, bases, and ferrous salts, as well as on thermolysis, have already been investigated by Emmons.¹¹ Our knowledge on these reactions has increased in the last decade but has remained within the scope of the early investigations.

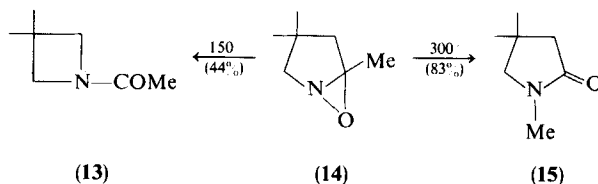
³⁸ M. Bucciarelli, I. Moretti, G. Torre, G. D. Andreotti, G. Bocelli, and P. Sgarabotto, *Chem. Commun.*, 60 (1976).

³⁹ C. Belzecki and D. Mortowicz, *Chem. Commun.*, 244 (1975).

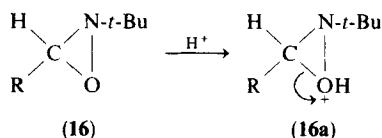
⁴⁰ C. Belzecki and D. Mortowicz, *J. Org. Chem.* **40**, 3878 (1975).

⁴¹ M. Bogucka-Ledóchowska, A. Konitz, A. Hempel, Z. Dauter, E. Borowski, C. Belzecki, and D. Mostowicz, *Tetrahedron Lett.*, 1025 (1976).

In the thermolysis of oxaziridines there is competitive formation of two acid amides, since in principle either substituent can migrate to nitrogen. In one case the dependence of the competing reactions on temperature was observed. At 150°C the bicyclic oxaziridine undergoes ring contraction with formation of the acylated azetidine, whereas methyl migration with formation of the pyrrolidone **15** predominates at 300°C.⁴²



Acid hydrolysis of oxaziridines was investigated kinetically and found to be of first order and H_0 -dependent.⁴² 2-*t*-Butyl oxaziridines with an alkyl or aryl group in position 3 (**16**) were studied. The acidity-rate-profile approximated a constant rate given by complete protonation of **16**. pK values are between +0.13 and -1.81, rate constants of hydrolysis in dilute perchloric acid at 25°C are $43.4 \times 10^{-3} \text{ min}^{-1}$ ($R = p$ -nitrophenyl) and $1.49 \times 10^{-3} \text{ min}^{-1}$ ($R = \text{phenyl}$). O-Protonation is assumed to be followed by C—O bond cleavage (**16a**). In the case of 3-alkyloxaziridines there is considerable competition from O—N bond cleavage.



Hydrolysis of 2-*t*-butyl-3-phenyloxaziridine is enhanced by a factor of 68 on addition of sodium dodecanoate, by a micellar effect.⁴³

Quaternization at nitrogen of an oxaziridine was achieved using methyl fluorosulfonate.⁴⁴

Owing to the easy transformation of oxaziridines into nitrones and hydroxylamines, oxaziridine formation can be inserted into multistep syntheses as a reliable stage. Usually oxaziridine formation is brought about by *m*-chloroperbenzoic acid, which is commercially available.^{45,46} For example,

⁴² L. S. Kaminsky and M. Lamchen, *J. Chem. Soc.*, 2128 (1967).

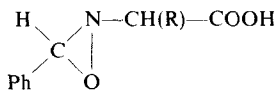
⁴³ B. C. Challis and A. R. Butler, *J. Chem. Soc. B*, 778 (1971); C.J. O'Connor, E. J. Fendler, and J. H. Fendler, *J.C.S. Perkin II*, 1900 (1973).

⁴⁴ P. Milliet, A. Picot, and X. Lusinchi, *Tetrahedron Lett.*, 1573 (1976).

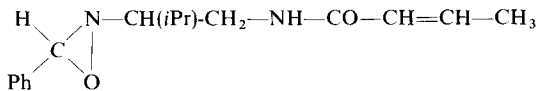
⁴⁵ A. Padwa, *Tetrahedron Lett.*, 2001 (1964).

⁴⁶ R. G. Pews, *J. Org. Chem.* **32**, 1628 (1967).

isomerization of oxaziridines is an important route to nitrones⁴⁷ and aliphatic nitroso compounds; *N*-hydroxyamino acids were prepared via oxaziridines **17**.^{48,49} Preparation of the oxaziridine **18**, followed by hydrolysis, was used in the synthesis of dopastine,⁵⁰ a naturally occurring hydroxylase inhibitor.

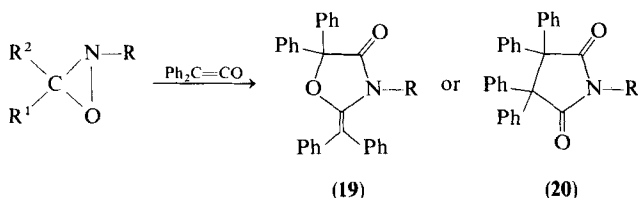


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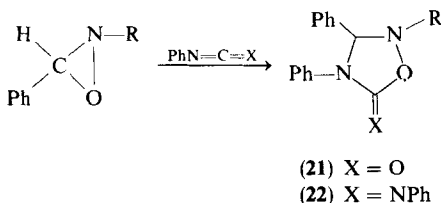


(18)

Some reactions of oxaziridines with heterocumulenes were described by Japanese authors. Two molecules of diphenylketene can form compounds **19** and **20**, inserting the group R—N of the oxaziridine. Formally the reaction may be represented as addition of an α -lactam to either the C=O or the C=C bond of diphenylketene. Depending on the substituents of the starting oxaziridine, types **19**⁵¹ or **20**⁵² predominate.



Phenyl isocyanate reacts with ring enlargement to give **21**, as does diphenyl carbodiimide to form **22**.⁵¹



⁴⁷ J. F. W. Keana and T. D. Lee, *J. Am. Chem. Soc.* **97**, 1273 (1975).

⁴⁸ T. Polonski and A. Chimiak, *Tetrahedron Lett.*, 2453 (1974).

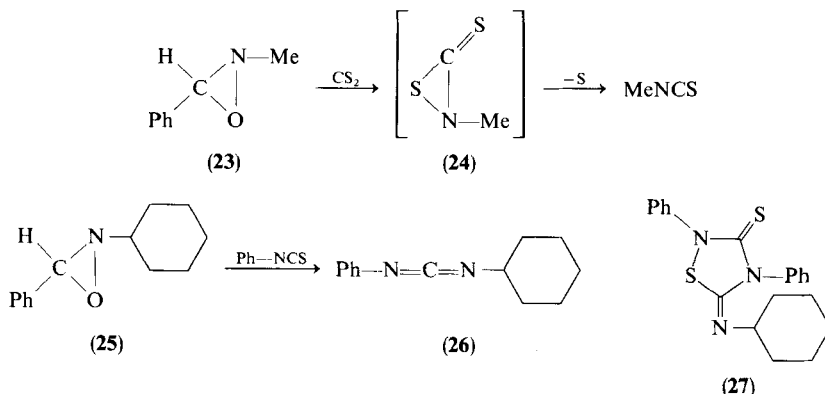
⁴⁹ J. Widmer and W. Keller-Schierlein, *Helv. Chim. Acta* **57**, 657 (1974).

⁵⁰ M. Ohno, H. Iinuma, N. Yagisawa, S. Shibahara, Y. Suhara, S. Kondo K. Maeda, and H. Umezawa, *Chem. Commun.*, 147 (1973).

⁵¹ M. Komatsu, Y. Ohshiro, H. Hotta, M. Sato, and T. Agawa, *J. Org. Chem.* **39**, 948 (1974).

⁵² Y. Ohshiro, T. Minami, K. Yasuda, and T. Agawa, *Tetrahedron Lett.*, 263 (1969).

Sulfur-containing heterocumulenes react with rupture of the N—O bond of the oxaziridine.⁵³ Carbon disulfide reacts at its boiling temperature to form, e.g., methyl isothiocyanate from oxaziridine **23**. Extrusion of sulfur, plausible from an intermediate like **24**, was observed.



Under more vigorous conditions, the isothiocyanates themselves react with oxaziridines. The carbodiimide **26** is formed from **25** and phenyl isothiocyanate. Under milder conditions the thiadiazolidinethione **27** was formed as the main product from the same reagents.

Homolytic cleavage of oxaziridines by ferrous salts, already described by Emmons,¹¹ is a useful source of alkyl radicals. From oxaziridine **28**, easily accessible from cyclohexanone and *N*-chloromethylamine,⁵⁴ on the action of ferrous salt, reaction products of radical **29** are obtained: In the presence of FeCl_2 ω -chlorohexanoic acid methylamide (**30**) is formed quantitatively;⁵⁵ in the absence of reaction partners, dimerization occurs to **31**.⁵⁶ As shown in a very careful investigation by Hawkins⁵⁷ in the case of the *N*-cyclohexyl compound, the dicarboxylic acid derivative is accompanied by appreciable quantities of branched-acid derivatives, formed by a radical rearrangement **29** \rightarrow **32**. The radical **29** adds to pyridine and gives rise, after rearomatization, to the formation of 70–80% of 2- and 4-substituted pyridine (**33**).⁵⁸

⁵³ M. Komatsu, Y. Ohshiro, K. Yasuda, S. Ichijima, and T. Agawa, *J. Org. Chem.* **39**, 957 (1974).

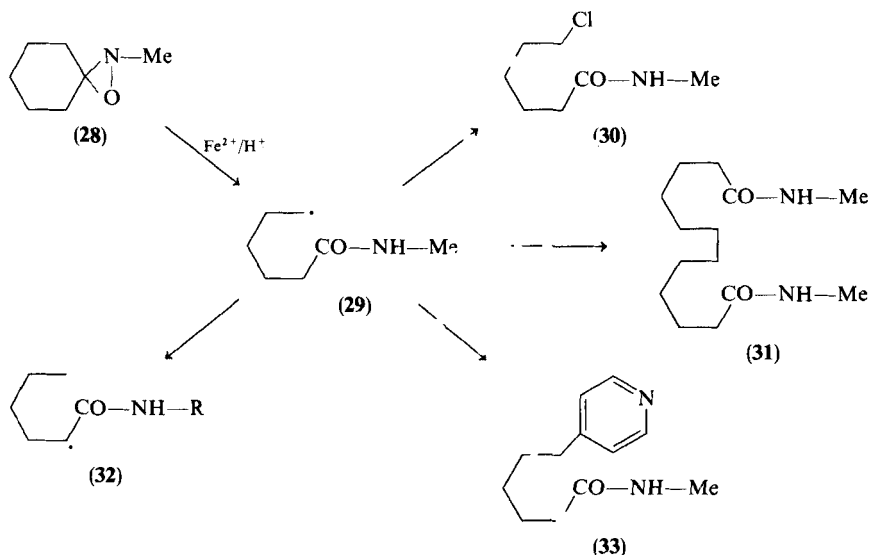
⁵⁴ E. Schmitz, R. Ohme, and D. Murawski, *Chem. Ber.* **98**, 2516 (1965).

⁵⁵ F. Minisci, M. Cecere, and R. Galli, *Chim. Ind. (Milan)* **50**, 225 (1968).

⁵⁶ E. Schmitz and D. Murawski, *Chem. Ber.* **98**, 2525 (1965).

⁵⁷ E. G. E. Hawkins, *J. Chem. Soc.*, 2155 (1973).

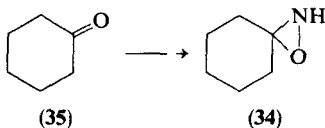
⁵⁸ F. Minisci, R. Galli, M. Cecere, V. Malatesta, and T. Caronna, *Tetrahedron Lett.*, 5609 (1968).



The system oxaziridine-ferrous salt has been proposed for initiation of vinyl polymerization.⁵⁹

D. OXAZIRIDINES UNSUBSTITUTED AT NITROGEN

Oxaziridines bearing no substituent at nitrogen were not, until recently, prepared by the peracid procedure. They became available only after the discovery of a novel oxaziridine synthesis, which instead of formally adding oxygen to a $\text{C}=\text{N}$ double bond consisted in adding an imino group to a $\text{C}=\text{O}$ double bond. The first compound of this type was prepared by Schmitz and Ohme⁶⁰ in 1961 by treating cyclohexanone with an alkaline solution of hydroxylamine-*O*-sulfonic acid. 3,3-Pentamethyleneoxaziridine (34) was formed (ca. 50% yield) in an extremely fast reaction.⁶¹ Analogous compounds were prepared from methyl ethyl ketone and benzaldehyde (yields ca. 30%).



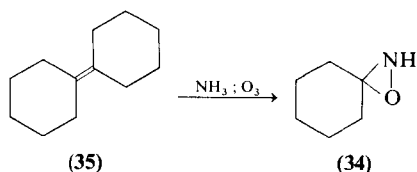
⁵⁹ S. Sakai, S. Fujii, M. Kitamura, and Y. Iskii, *J. Polym. Sci., Part B* **3**, 955 (1965).

⁶⁰ E. Schmitz and R. Ohme, *Angew. Chem.* **73**, 708 (1961).

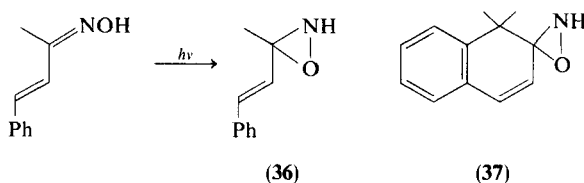
⁶¹ E. Schmitz, R. Ohme, and S. Schramm, *Chem. Ber.* **97**, 2521 (1964).

Later, solutions of **34** were prepared in up to 85% yield starting with cyclohexanone and chloramine, or simply by treating cyclohexanone with solutions of ammonia and sodium hypochlorite.⁶² In the presence of cyclohexanone, chloramine reacts faster by at least three powers of 10 with hydroxyl ion, compared with the reaction in the absence of the ketone.

Formation of **34** was also observed on ozonation of the olefin **35** in the presence of ammonia.⁶³



A further useful preparation consists in photoisomerization of oximes.⁶⁴ As had often been supposed, oximes, especially α,β -unsaturated ones, isomerize with formation of oxaziridines: **36** was formed in 50% yield from benzylideneacetone oxime on irradiation, and **37** could be prepared from both *Z* and *E* oxime isomers.



A recent publication⁶⁵ describes the preparation by the peracid method of oxaziridines unsubstituted at nitrogen. The ketimines used were of benzophenone and di-*n*-butyl ketone.

In some reactions the compounds unsubstituted at nitrogen proved to be typical oxaziridines. So the classification as oxaziridines was never a problem. They can be cleaved by hydrolysis to give carbonyl compounds and hydroxylamine and can easily be reduced by iodide in acid solution to form iodine, the carbonyl compound, and ammonia. *N*-Alkylation by *t*-butyl chloride leads to the known *N*-*t*-butyloxaziridine.⁶¹ By the action of ferrous salts the diamide of dodecanedicarboxylic acid is formed, in analogy to the formation of **31**.

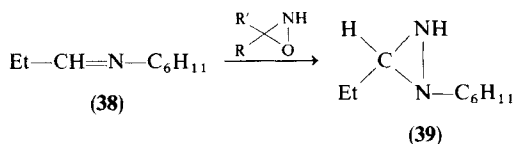
⁶² E. Schmitz, R. Ohme, H. Striegler, H.-U. Heyne, and S. Schramm, German Patent 1,961,474 (1970)[*CA* 73, 45492 (1970)]; *J. Prakt. Chem.* **319**, 195 (1977).

⁶³ M. Schulz, D. Becker, and A. Rieche, *Angew. Chem.* **77**, 548 (1965).

⁶⁴ T. Oine and T. Mukai, *Tetrahedron Lett.*, 157 (1969); T. Oine, T. Mukai, and K. Kikuchi, *Sci. Rep. Tohoku Univ., Ser. I* **54**, 193 (1971).

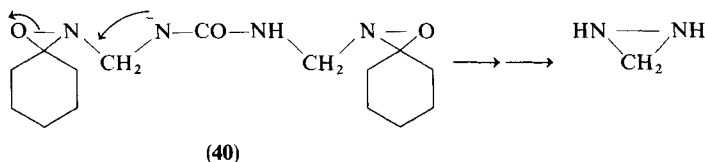
⁶⁵ R. F. Hudson, A. J. Lawson, and K. A. F. Record, *Chem. Commun.*, 322 (1975).

What was not foreseeable from experience with the *n*-alkyl compounds was the low stability of the N-unsubstituted oxaziridines. As long as they are kept in solution they are fairly stable, but they decompose rapidly on attempted isolation. The formation of nitrogen and ammonia as well as of some hydrazine points to an analogy with NH-transferring agents like chloramine or hydroxylamine *O*-sulfonic acid, which in fact bear some analogy to **34**. Aniline is aminated to give phenylhydrazine,⁶¹ and the Schiff base **38** is aminated to give the diaziridine **39**.

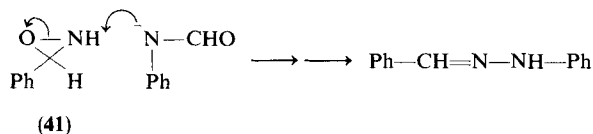


It was observed that the last reaction works only when basic impurities are trapped by some added acetic acid or carbon dioxide. Later this stabilization of oxaziridine solutions by carbon dioxide was claimed in a patent.⁶⁶

The amination occurs intramolecularly when the oxaziridine **40**, formed from **34** and dimethylol urea, is treated with strong alkali. This amination gives rise to the parent compound of the diaziridines.⁶⁷



Further aminations are the formation of cyclohexanone oxime *O*-methyl-ether from **34** and methanol,⁶⁸ and of benzaldehyde phenylhydrazine from 3-phenyloxaziridine **41** and formanilide.⁶⁸

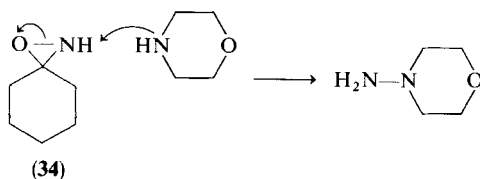


Amination of secondary amines proceeds especially smoothly. Morpholine and diethylamine are aminated by solutions of **34** within minutes at room temperature. Dialkylhydrazines are formed in yields better than 90%.

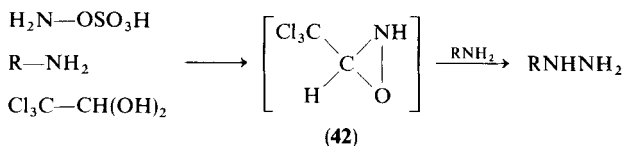
⁶⁶ Y. Kobayashi, Japanese Patent 71 45,242 [CA **78**, 111284 (1973)].

⁶⁷ E. Schmitz, R. Ohme, and S. Schramm, *Tetrahedron Lett.*, 1857 (1965).

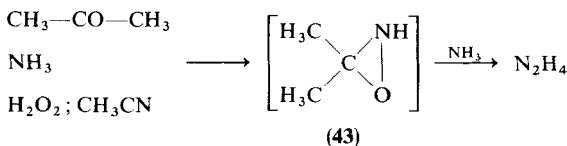
⁶⁸ E. Schmitz, R. Ohme, and S. Schramm, *Justus Liebigs Ann. Chem.* **702**, 131 (1967).



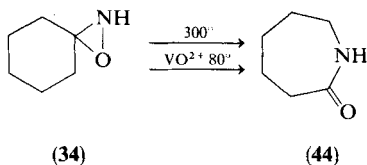
The smooth uptake and transfer of NH groups by carbonyl compounds gives rise to catalytic reaction sequences. In the known synthesis of alkylhydrazines from amines and hydroxylamine-*O*-sulfonic acid,⁶⁹ added chloral leads to trichloromethyloxaziridine **42**, which subsequently transfers its NH-group to the amine.⁷⁰



This type of smooth NH transfer is probably the crucial step of a novel technical hydrazine synthesis,⁷¹ in which a mixture of hydrogen peroxide and acetonitrile acts on an acetone-ammonia mixture. 3,3-Dimethyloxaziridine (**43**) is supposed to be formed, and immediately to transfer its NH group to ammonia.



Thermal isomerization of oxaziridines into amides and lactams, one of the most widespread reactions of oxaziridines, fails with the compounds unsubstituted at nitrogen. Obviously NH-transfer reactions predominate. Lactam formation from **34** could be brought about only by a kind of flash pyrolysis⁷²: slowly adding **34** to preheated paraffin at 300°C gave caprolactam **44** (85%).



⁶⁹ G. Gever and K. Hayes, *J. Org. Chem.* **14**, 813 (1949).

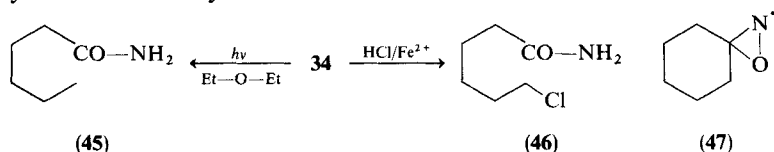
⁷⁰ W. Flamme, Dissertation, Humboldt-Universität, Berlin (1969).

⁷¹ J. P. Schirrmann and F. Weiss, *Tetrahedron Lett.*, 635 (1972).

⁷² E. Schmitz, R. Ohme, H. Striegler, S. Schramm, and H.-U. Heyne, GDR Patent 81, 656 (1968).

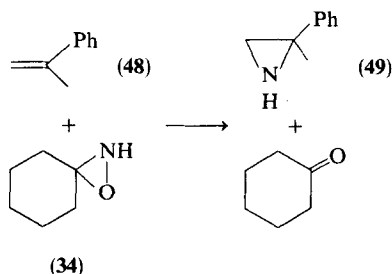
However, **34** is converted into caprolactam under much milder conditions in the presence of catalytic amounts of vanadium compounds. Rearrangement (88%) is brought about by vanadium acetylacetonate in boiling benzene.⁷³

Irradiation as well as the action of ferrous salts results in homolytic cleavage of the three-membered ring of **34**. By photolysis of ethereal solutions of **34** in the presence of triplet sensitizers, Kobayashi⁷⁴ obtained 47% *n*-caproic amide **45**; thus the conversion had involved uptake of two atoms of hydrogen. Striegler and Timm converted **34** into 6-chlorocaproic amide **46** by ferrous salt in hydrochloric acid.⁷⁵



An oxaziridinyl radical (**47**) is formed from 3,3-pentamethylenesoxaziridine with silver oxide or lead dioxide.⁷⁶

It was recently demonstrated that **34** transfers its NH group to olefins. Aziridine **49** is obtained in 46% yield from α -methylstyrene **48** by 3 hours of heating with a solution of **34** in toluene. The same reaction was observed with styrene and its ring substitution products, indene, 1,1-diphenylethylene, and also norbornene and acrylonitrile.⁷⁷



By use of appropriate olefins, the reaction was proved to proceed stereospecifically. Simple aliphatic olefins do not react or react only with poor yields. With cyclohexene there is competitive subsequent amination to give

⁷³ E. Schmitz, H. Striegler, H.-U. Heyne, K.-P. Hilgetag, H. Dilcher, and R. Lorenz, *J. Prakt. Chem.* **319**, 274 (1977).

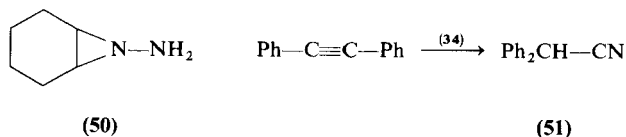
⁷⁴ Y. Kobayashi, Japanese Patent 73 05,711 (1973) [*CA* **78**, P124077 (1973)].

⁷⁵ H. Striegler and D. Timm, GDR Patent 98,913 (1973) [*CA* **80**, 59508 (1974)].

⁷⁶ T. A. B. M. Bolsman and T. J. DeBoer, *Tetrahedron* **31**, 1019 (1975).

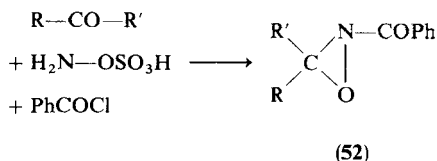
⁷⁷ E. Schmitz and K. Jähnisch, *Khim. Geterotsikl. Soedin.*, 1629 (1974).

N-aminoaziridine **50**. Diphenylacetylene, by uptake of NH and phenyl migration, yields diphenylacetoneitrile **51**.

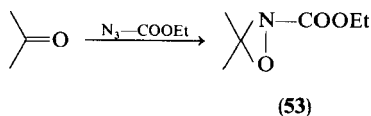


E. 2-ACYLOXAZIRIDINES

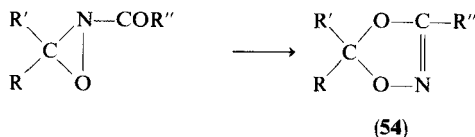
2-Acyloxaziridines are easily obtained from compounds unsubstituted at nitrogen by reaction with acid chlorides or isocyanates.⁷⁸ Acylation proceeds so smoothly that, in the amination of carbonyl compounds, oxaziridine compounds are obtained in better yields on addition of acid chlorides than in the absence of the acylating agent. With aliphatic aldehydes, amination does not succeed at all except in the presence of benzoyl chloride. Proof of structure comes from reduction by iodide to give the acid amide and carbonyl compound.



Oxaziridine syntheses by nitrene addition to a carbonyl group, which in the past had failed repeatedly, was described recently by Japanese authors to occur on photolysis of ethyl azidoformate in acetone. It yielded *N*-ethoxycarbonyloxaziridine **53**.⁷⁹

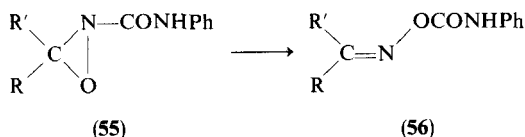


The acyl group as an additional element of structure gives rise to some rearrangements. All the carboxylic acid derivatives so far investigated undergo ring enlargement to dioxazoles **54** on heating.⁷⁸

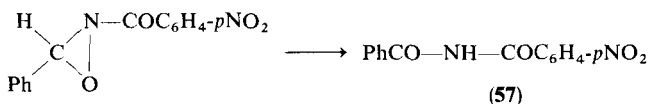


⁷⁸ E. Schmitz and S. Schramm, *Chem. Ber.* **100**, 2593 (1967).

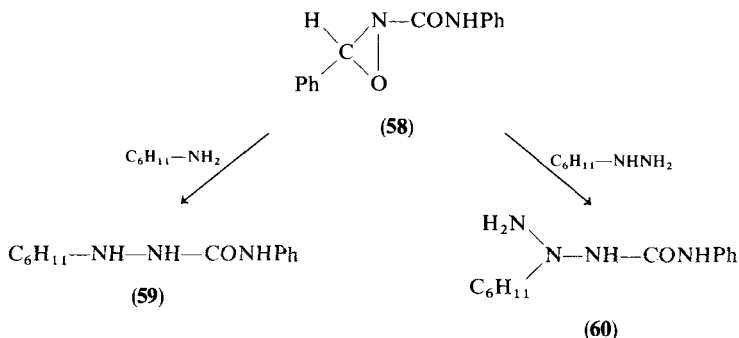
⁷⁹ T. Hiyama, H. Taguchi, S. Fujita, and H. Nozaki, *Bull. Chem. Soc. Jpn.* **45**, 1863 (1972).



The isocyanate adducts **55** isomerize to form the *O*-acylated oximes **56**.⁷⁸ In one case isomerization to diacylimide **57** was observed in the presence of cyclohexylamine.⁷⁸



Some 2-acyloxaziridines are remarkable because of their tendency to transfer an acylamino group. For example, the 3-phenyl compound **58** aminates cyclohexylamine with formation of the substituted semicarbazide **59**.⁸⁰



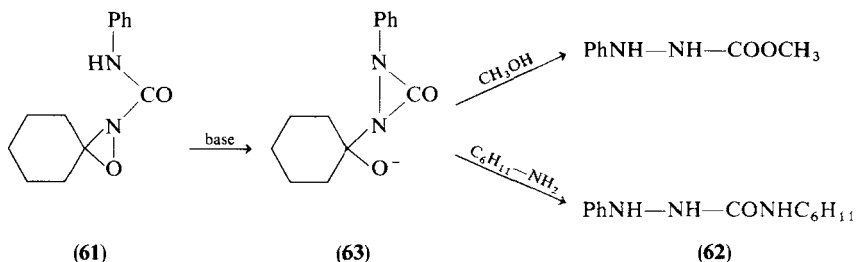
In these reactions the 2-acyloxaziridines do not act as nitrene precursors. The amination reactions proceed under mild conditions, at temperatures of 0° or slightly above, in the course of a few minutes or even seconds. The starting compounds are quite stable under these conditions in the absence of a nucleophile. Even hydrazines can be aminated to form very unstable triazanes. So cyclohexylhydrazine forms crystalline **60**.⁸¹

In competition with these amination reactions, intramolecular aminations can occur, and they become the main reaction in certain cases. The oxaziridine **61**, derived from cyclohexanone, reacts with methoxide to give the phenylhydrazine carboxylic ester, and with cyclohexylamine to the sub-

⁸⁰ E. Schmitz, S. Schramm, and R. Ohme, *J. Prakt. Chem.* **36**, 86 (1967).

⁸¹ E. Schmitz, S. Schramm, and H. Fechner-Simon, *Justus Liebigs Ann. Chem.* **725**, 1 (1969).

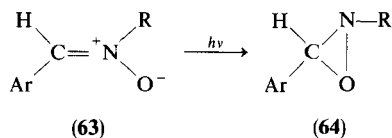
stituted semicarbazide **62**.⁸² Diaziridinone **63** is postulated to be the common intermediate, formed by intramolecular substitution from deprotonated **61**.



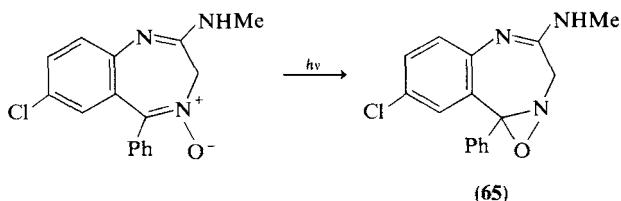
The formation of the isomeric semicarbazides **59** and **62** from cyclohexylamine (**59** is a derivative of cyclohexylhydrazine, and **62** is a derivative of phenylhydrazine) is surprising, since the same type of starting material, **58** and **61**, respectively, is allowed to react with the same reagent.

F. PHOTOCHEMICAL FORMATION AND TRANSFORMATION OF OXAZIRIDINES

Nitrones **63** on illumination yield the isomeric oxaziridines **64**, as was shown shortly after the discovery of this class of compound. Although many oxaziridines decompose on illumination, their occurrence was demonstrated unambiguously, in some cases by isolation.



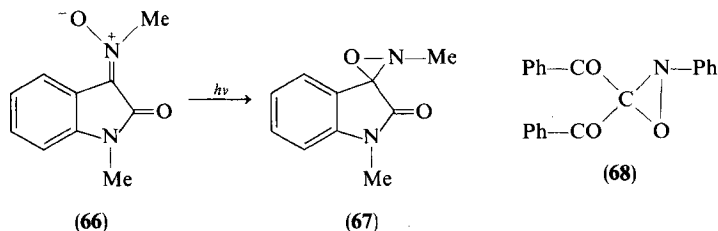
During the last 10 years many additional oxaziridines have been isolated after photolysis of nonaromatic nitrones. The three-membered ring isomers of heteroaromatic *N*-oxides proved to be too reactive for direct detection but



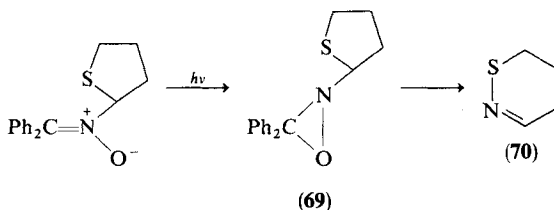
⁸² E. Schmitz, R. Ohme, and S. Schramm, *Chem. Ber.* **100**, 2600 (1967).

are plausible in many cases as intermediates. Isomerization products of benzdiazepine *N*-oxides were shown to be very stable,⁸³⁻⁸⁵ for example **65**.⁸³

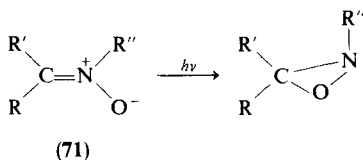
Nitrone **66**, derived from isatin, yields **67** on illumination,⁸⁶ and a diacyl nitrone forms the isomeric oxaziridine **68**.⁸⁷



Oxaziridines such as **69** are formed by illumination of sulfur-containing nitrones, and they decompose at 100°C by intramolecular S—N bond formation: **69** yields the thiazine **70**.⁸⁸



The steric course of oxaziridine formation was investigated by Splitter *et al.* Only one out of two feasible disrotatory processes of nitrone **71** is observed, bringing the outer substituents R' and R'' on the same side of the ring.⁸⁹ An observed unspecificity of ring closure products may be accounted for by prior E-Z isomerization of the nitrone.



⁸³ G. F. Field and L. H. Sternbach, *J. Org. Chem.* **33**, 4438 (1968).

⁸⁴ O. Hromatka, M. Knollmüller, and D. Binder, *Monatsh. Chem.* **99**, 1117 (1968).

⁸⁵ B. J. Hester, U.S. Patent 3,681,343 (1972) [*CA* **77**, 126707 (1972)].

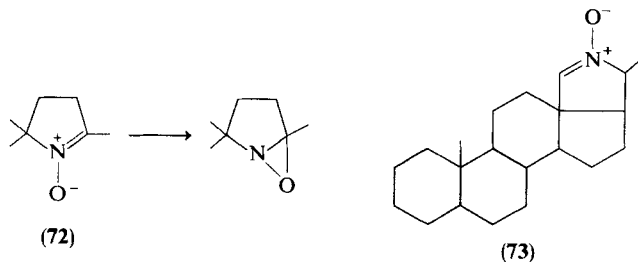
⁸⁶ H. G. Aurich and U. Grigo, *Chem. Ber.* **109**, 200 (1976).

⁸⁷ M. L. Scheinbaum, *Tetrahedron Lett.*, 4221 (1969).

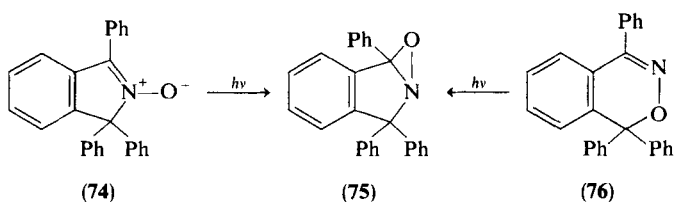
⁸⁸ W. M. Leyshon and D. A. Wilson, *J.C.S. Perkin I*, 1925 (1975).

⁸⁹ J. S. Splitter, T. M. Su, H. Ono, and M. Calvin, *J. Am. Chem. Soc.* **93**, 4075 (1971).

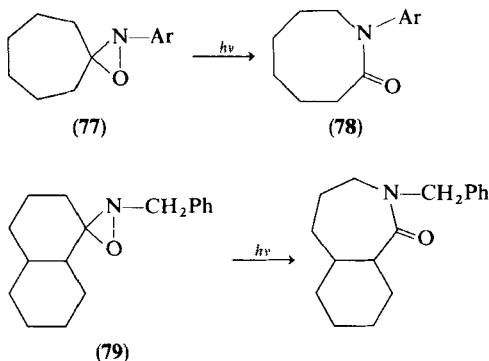
The conservation of the *cis* arrangement of two substituents during ring closure favors formation of bicyclic oxaziridines, which has been observed repeatedly, for example, in the illumination of pyrroline *N*-oxides **72**⁹⁰ or the derivative **73** of a steroidal alkaloid.⁹¹



The oxaziridine **75** was formed by illumination not only of the nitron **74**, but also of the oxime ether **76**.⁹²



In most cases irradiation of oxaziridines leads to the isomeric acid amides. The investigation of this reaction must take into account that acid amide



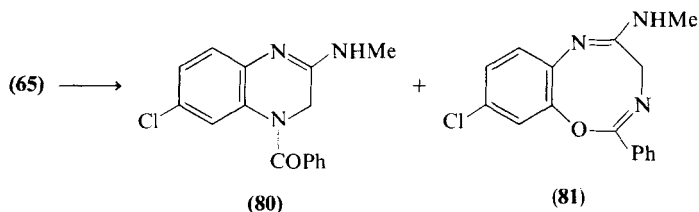
⁹⁰ L. S. Kaminsky and M. Lamchen, *J. Chem. Soc. C*, 2295 (1966).

⁹¹ J. Parello, R. Beugelmans, P. Milliet, and X. Lusinchi, *Tetrahedron Lett.*, 5087 (1968).

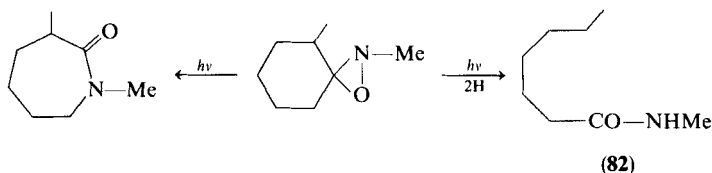
⁹² B. Singh, *J. Am. Chem. Soc.* **90**, 3893 (1968).

formation may also occur thermally, at temperatures above 100° with *N*-alkyloxaziridines, and at room temperature with certain *N*-aryloxaziridines. However, the photoformation of *N*-aryllactams **78** from spirooxaziridines **77**⁹³ as well as lactam formation from the aliphatic oxaziridine **79**⁹⁴ occur under conditions where the starting compounds are thermally stable.

Besides the well known competition of migration of the substituents from C-3, competing migration to either oxygen or nitrogen was observed. Sternbach and co-workers detected imino ethers as products of migration from carbon to oxygen: Photolysis of **65** yielded a mixture of **80** and **81**⁸³ and an analogous reaction was observed with the corresponding 1,4-diazepin-2-one.⁹⁵



When the H-donor isopropanol is used as solvent, a side reaction is apparent, proceeding with uptake of 2 H from the solvent and formation of the open-chain acid amide **82** from a spirooxaziridine.⁹⁶



During photolysis of some *N*-phenyloxaziridines, the occurrence of azobenzene was observed.⁹⁷ The appearance of phenylnitrene was shown by electron spin resonance (ESR) spectroscopy⁹⁸ and by trapping of its ring enlargement product by diethylamine (**83**).⁹⁹

⁹³ M. Fischer, *Tetrahedron Lett.*, 2281 (1969).

⁹⁴ E. Desherces, M. Riviere, J. Parelo, and A. Lattes, *C. R. Acad. Sci., Ser. C* **275**, 581 (1972).

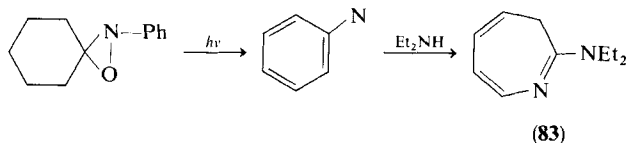
⁹⁵ R. Y. Ning, G. F. Field, and L. H. Sternbach, *J. Heterocycl. Chem.* **7**, 475 (1970).

⁹⁶ F. Oliveros-Desherces, M. M. Riviere, J. Parelo, and A. Lattes, *Tetrahedron Lett.*, 851 (1975).

⁹⁷ H. Mauser and H. Bokranz, *Z. Naturforsch., Teil B* **24**, 477 (1969).

⁹⁸ J. S. Splitter and M. Calvin, *Tetrahedron Lett.*, 1445 (1968).

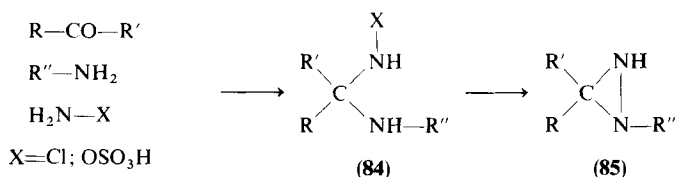
⁹⁹ E. Meyer and G. W. Griffin, *Angew. Chem., Int. Ed. Engl.* **6**, 634 (1967).



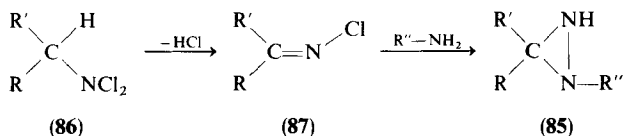
III. Diaziridines

A. SYNTHESIS OF DIAZIRIDINES

The majority of diaziridine syntheses proceed by intramolecular electrophilic amination in a geminal compound **84**,¹⁰⁰ an aminallike^{100a} compound from an amine, a carbonyl compound, and an electrophilic aminating agent like chloramine or hydroxylamine-*O*-sulfonic acid. The different ways of diaziridine synthesis differ mainly in the timing of the build-up of this geminal intermediate **84**, from which the diaziridine **85** is isolated.



To the original methods, like reaction of Schiff bases with chloramine or hydroxylamine-*O*-sulfonic acid or the simultaneous action of chloramine and ammonia on carbonyl compounds, have been added new ways, for example, the reaction of *N*-chloroketimines **87** with amines.^{101,102}



Since *N*-chloroketimines **87** are easily obtained from *N*-dichloroamines **86** by base-promoted elimination of HCl, it is advantageous to allow **86** to react with an excess of a primary amine.^{103,104}

¹⁰⁰ E. Schmitz, *Usp. Khim.* **45**, 54 (1976).

^{100a} Although diaziridines can be prepared from many starting materials, the report "Diaziridines from Animals" is believed to involve a misprint [*CA* **65**, 8887 (1966)].

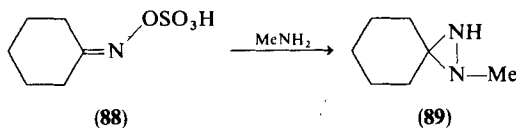
¹⁰¹ D. Murawski, Dissertation, Humboldt-Universität, Berlin (1965).

¹⁰² J. J. Fuchs, U.S. Patent 3,290,289 (1966) [*CA* **66**, 55472 (1967)].

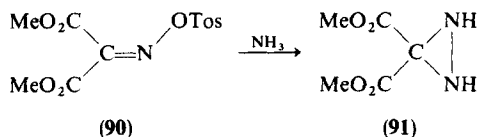
¹⁰³ E. Schmitz and W. Flamme, see Flamme,⁷⁰ p. 32.

¹⁰⁴ K. W. Eichenhofer and R. Schliebs, German Patent 2,338,761 (1975) [*CA* **83**, 28209 (1975)].

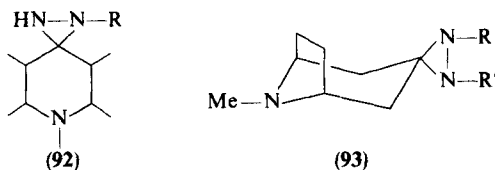
A novel variation from hydroxylamine-*O*-sulfonic acid starts with the oxime-*O*-sulfonic acid, e.g., **88**, which gives the diaziridine by addition of an amine followed by elimination of sulfuric acid. Thus **89** is obtained in 52% yield.²



During the last years the reaction of *O*-sulfonylated oximes with amines was applied repeatedly.¹⁰⁵⁻¹⁰⁷ It gives diaziridines even from electron-poor carbonyl compounds, which had not been accessible so far. For example, diaziridine **91** is obtained from the *O*-tosyl oxime of mesoxalic ester (**90**).¹⁰⁷



Smooth diaziridine formation even in the presence of additional functional groups in the starting ketone, allowed many individual diaziridines to be made for pharmacological testing. More than fifty compounds of types **92** and **93** with the basic piperidone and tropine structures, were synthesized.¹⁰⁸



In the steroids diaziridine formation occurs most successfully in the sterically unhindered 3-position,¹⁰⁹ less favorably in the 2-position, in which formation of an aminal-like intermediate is hindered by 1,3-diaxial interaction with a methyl group. In the sterically most hindered 17-position, diaziridine synthesis may be effected by formation of a Schiff base with cyclohexylamine, thus eliminating water before introduction of the aminating

¹⁰⁵ Y. V. Zeifman, E. G. Abduganiev, E. M. Rokhlin, and I. L. Knunyants, *Izv. Akad. Nauk. SSSR, Ser. Khim.*, 2737 (1972).

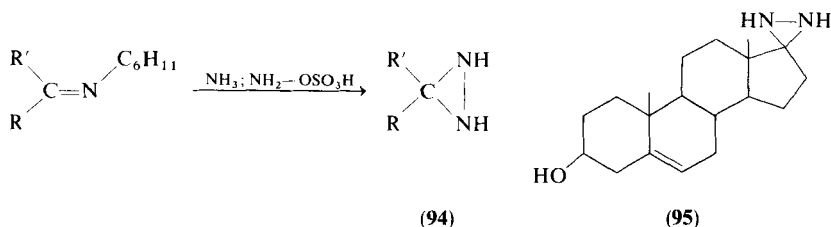
¹⁰⁶ S. S. Novikov, L. I. Khmel'nitskii, and A. N. Mikhailuk, USSR Patent 469,699 (1975) [CA 83, 114364 (1975)].

¹⁰⁷ R. G. Kostyanovskii, G. V. Shustov, and G. V. Markov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2823 (1974).

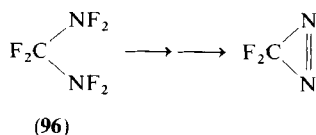
¹⁰⁸ P. Borrevang and E. Guddal, French Patent 1,562,790 (1969) [CA 72, 66923 (1970)].

¹⁰⁹ R. F. R. Church, A. S. Kende, and M. J. Weiss, *J. Am. Chem. Soc.* 87, 2665 (1965).

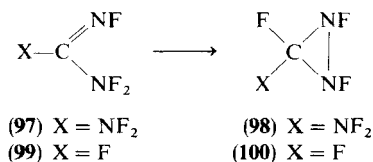
agent. Subsequent reaction with ammonia and hydroxylamine-*O*-sulfonic acid leads to the diaziridine **94**,¹¹⁰ e.g., in the case of the steroidal diaziridine **95**.



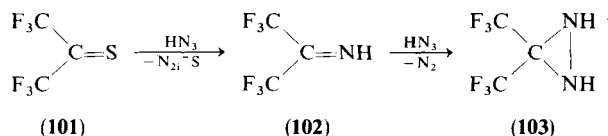
The general pattern of diaziridine synthesis is probably also followed by three-membered ring formation from perfluorinated aminals¹¹¹ as well as by a diaziridine synthesis from hydrazoic acid.¹¹² In the course of the difluorodiazirine synthesis of Mitsch,¹¹¹ perfluoromethylenediamine **96** is defluorinated by ferrocene.



Preparation of the diaziridine **98** from pentafluoroguanidine **97** as well as that of diaziridine **100** from tetrafluoroformamidine **99** by the action of alkali fluoride at -80°C , were described by Firth.¹¹³



The diaziridine formation mentioned above to occur with HN₃¹¹² was observed when the perfluorinated thioketone **101** was treated with HN₃



¹¹⁰ American Cyanamid Co., Netherlands Patent 6,509,356 (1966)[CA **65**, 3942 (1966)].

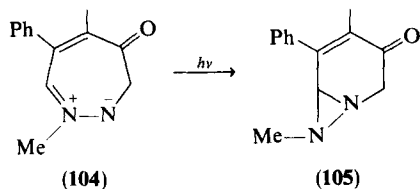
¹¹¹ R. A. Mitsch, *J. Heterocycl. Chem.* **1**, 59 (1966); *J. Org. Chem.* **33**, 1847 (1968).

¹¹² W. J. Middleton, U.S. Patent 3,226,439 (1965)[CA **64**, 9597 (1966)].

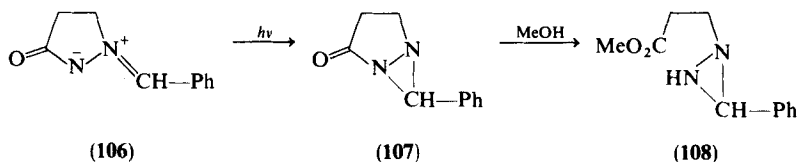
¹¹³ W. C. Firth, *J. Org. Chem.* **33**, 3489 (1966).

at -15°C . Besides the imine **102**, diaziridine **103** was obtained as a product of further reaction.

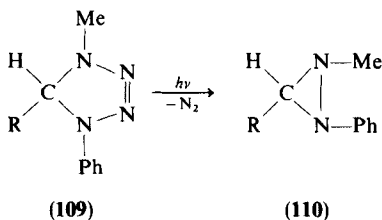
A photochemical diaziridine synthesis, analogous to the photoisomerization of nitrones, was worked out at suitable azomethine imines. By the action of sunlight, **104** is isomerized to the unstable diaziridine **105** in nearly 80% yield.¹¹⁴



An almost quantitative diaziridine photosynthesis from azomethine imines was described by Schulz and West.¹¹⁵ For example, **106** yields the isomeric diaziridine **107** on UV-irradiation in *t*-butanol, but the diaziridine **108** is the result of a subsequent deacylation in methanol.



A further photochemical diaziridine synthesis starts from tetrazolines like **109**, which on irradiation lose nitrogen. In particular, the almost unknown *N*-aryldiaziridines became accessible by this procedure.¹¹⁶



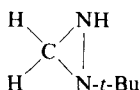
A high inversion barrier at nitrogen was found for diaziridines, which parallels the configurational stability at oxaziridine nitrogen. It was first discovered from NMR data and was proved by separation into *E* and *Z* isomers and finally by obtaining optically active diaziridines.

¹¹⁴ M. G. Pleiss and J. A. Moore, *J. Am. Chem. Soc.* **90**, 4738 (1968).

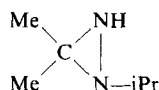
¹¹⁵ M. Schulz and G. West, *J. Prakt. Chem.* **312**, 161 (1970).

¹¹⁶ T. Akiyama, T. Kitamura, T. Isida, and M. Kawanisi, *Chem. Lett.*, 185 (1974) [*CA* **80**, 94932 (1974)].

The first detailed NMR investigation of diaziridines came as a common effort of several research groups.¹¹⁷ Nonequivalence of the ring protons of **111**, as a result of their *cis* and *trans* relationship to the *t*-butyl group, was demonstrated. A minimum value for the inversion barrier was based on the observation that there was no fast inversion in the range of thermal stability of the compound. The minimum value was 23 kcal/mol in the case of **112**. This prompted efforts toward the separation of isomers.

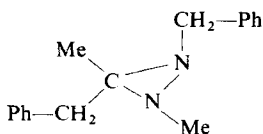


(111)

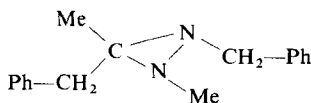


(112)

Successful separation of isomers was reported shortly afterwards by Mannschreck and Seitz.¹¹⁸ The diaziridine mixture obtained from benzyl methyl ketone, benzylamine, and methylhydroxylamine-*O*-sulfonic acid could be separated by thin-layer chromatography into isomers **113a** and **113b**. At 70°C the half-life of one individual isomer was 431 minutes, the barrier of inversion being 27.4 kcal/mol. The existence of configurational



(113a)



(113b)

isomers of diaziridines has been observed a number of times.^{116,119,120} An extensive investigation which included N-acylated diaziridines was carried out by Kostyanovskii and co-workers.¹²⁰ To obtain optically active diaziridines, an excess of **89** was allowed to react with optically active α -phenethyl isocyanate. Unreacted diaziridine proved to be optically active. The isocyanate adduct was recrystallized to give a pure diastereomer of **114**. A barrier of inversion of 28 kcal/mol follows from the kinetic data of racemization of **89**.¹²¹

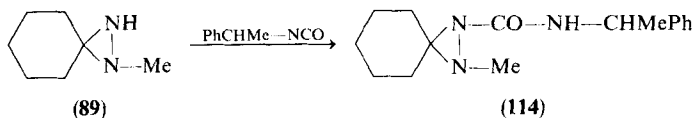
¹¹⁷ A. Mannschreck, R. Radeaglia, E. Gründemann, and R. Ohme, *Chem. Ber.* **100**, 1778 (1967).

¹¹⁸ A. Mannschreck and W. Seitz, *Angew. Chem., Int. Ed. Engl.* **8**, 212 (1969).

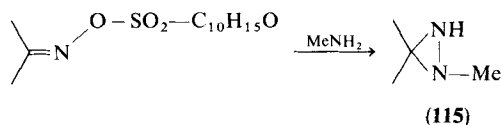
¹¹⁹ A. Nabeya, Y. Tamura, T. Kodama, and Y. Iwakura, *J. Org. Chem.* **38**, 3758 (1973).

¹²⁰ R. G. Kostyanovskii, K. S. Zakharov, M. Zaripova, and V. F. Rudtchenko, *Tetrahedron Lett.*, 4207 (1974); *Izv. Akad. Nauk SSSR, Ser. Khim.* 875 (1975).

¹²¹ R. G. Kostyanovskii, A. E. Polaykov, G. V. Shustov, K. S. Zakharov, and V. I. Markov, *Dokl. Akad. Nauk SSSR* **219**, 873 (1974).



Recently there was a report on the asymmetric synthesis of diaziridines.¹²² For example, on reaction of camphor-sulfonylated acetone-oxime with methylamine, optically active **115** is formed with an optical purity of 10%

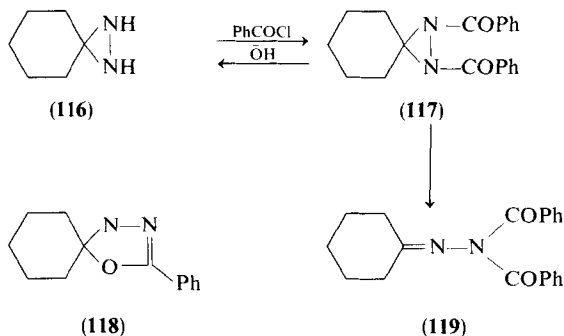


The formation of optically active **115** demonstrates that the chiral leaving group takes part in the rate-determining step of the diaziridine synthesis, which is an argument against a nitrene intermediate.

B. REACTIONS OF DIAZIRIDINES

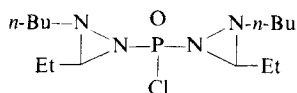
Diaziridines are more stable toward acids than expected from comparison with simple amins. Alkali is without action even in hot solution; acid hydrolysis requires reaction times between 1 hour and some weeks at room temperature, according to the nature of the substituents at the ring carbon. So it is possible to carry out reactions at nitrogen with retention of the three-membered ring.

Reaction with isocyanates or acid chlorides leads to *N*-acyldiaziridines. In contrast to an earlier report¹ that ring-enlarged products like **118** are

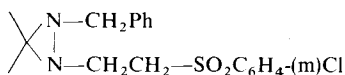


¹²² R. G. Kostyanovskii, G. E. Shustov, A. I. Mischtschenko, and W. I. Markov, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 2026 (1976).

formed in acylation reactions of some diaziridines, the diaziridine structure is stable during acylation.¹²³ The NMR spectrum of **117** shows two identical phenyl moieties; alkali cleaves it to the starting diaziridine. Thermally, **117** rearranges with ring opening and acyl migration to form **119**. Phosphorus oxychloride also reacts with conservation of the three-membered ring, e.g., with formation of **120**.¹²⁴



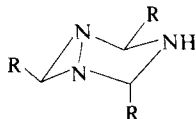
(120)



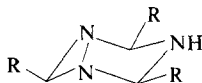
(121)

Alkylation by simple alkylating agents seems not to have been investigated, but hydroxyalkylation by epoxides,¹²⁵ cyanoethylation,¹²⁶ addition of methyl vinyl ketone¹²⁷ as well as of vinyl sulfones, e.g., with formation of **121**,¹²⁸ have been reported.

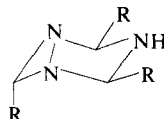
Further reaction of diaziridines is responsible for the formation of bicyclic compounds **122a-c** from aldehydes, chloramine and ammonia. The isomers **122a** and **122b** (R = various alkyl, aryl, and aralkyl groups) are obtained in a kinetically controlled reaction; work-up in the presence of ammonium chloride yields an additional isomer **122c** as a result of thermodynamic control.¹²⁹



(122a)



(122b)



(122c)

Cleavage of diaziridines to a carbonyl compound and hydrazine or a substituted hydrazine can be carried out with almost any diaziridine. In order not to obtain the hydrazine as a solution of its salt, techniques were elaborated to transform dialkyldiaziridines from either acetone or butanone into hydrazones under the influence of catalysts and to trap them as azines

¹²³ E. Schmitz, D. Habisch, and E. Gründemann, *Chem. Ber.* **100**, 142 (1967).

¹²⁴ C. Szántay, Z. F. Chmielewicz, and T. J. Bardos, *J. Med. Chem.* **10**, 101 (1967).

¹²⁵ M. D. Hinchliffe and J. Miller, British Patent 1,085,794 (1967) [*CA* **68**, 29243 (1968)].

¹²⁶ J. Miller, British Patent 1,081,292 (1967) [*CA* **68**, 114071 (1968)].

¹²⁷ V. N. Yandovskii and T. K. Klindukhova, *Zh. Org. Khim.* **10**, 1510 (1974).

¹²⁸ H. Dorn and K. H. Walter, *Justus Liebigs Ann. Chem.* **720**, 98 (1969).

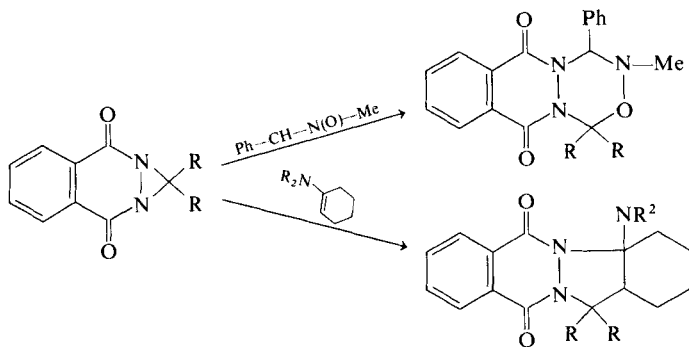
¹²⁹ A. T. Nielsen, D. W. Moore, R. L. Atkins, D. Mallora, J. D. Pol, and J. M. LaBerge, *J. Org. Chem.* **41**, 3221 (1976).

by added excess ketone.^{130,131} The tedious evaporation of diluted salt solutions was thus avoided in the large-scale production of hydrazine.

With regard to the simple diaziridine synthesis under large-scale conditions from ketone, ammonia, and chlorine,^{132,133} some patents claim a direct preparation of hydrazine products by reaction of diaziridines with suitable reagents. For example, hydrazine dicarboxylic acid diamide is obtained directly from 3-ethyl-3-methyldiaziridine and urea in acidic solution.¹³⁴ The reaction conditions, however (some hours at 70°–80°C), point to acid hydrolysis prior to reaction with urea.

Maleic hydrazide, an herbicide, may also be prepared from a diaziridine; it is formed by the action of maleic anhydride.¹³⁵

A series of reactions of diaziridines formally involves combination of a C—N—N group, formed by ring opening of a diaziridine, with a reaction partner, e.g., a nitron¹³⁶ or an enamine,¹³⁷ as formulated in Scheme 1.



SCHEME 1

In the reaction of 3,3-pentamethylenediaziridine **116** with diphenylcyclopropanone the C—N—N moiety can add either to the carbonyl group, to give **123**, or to the ring-opened cyclopropanone to give **124**.^{138,139}

¹³⁰ S. R. Paulsen, German Patent 1,126,395 (1962) [CA 57, 9857 (1962)].

¹³¹ Otsuka Chemical Drugs Co., Japanese Patent 71 02,008 (1971) [CA 74, P124828 (1971)].

¹³² S. R. Paulsen and G. Huck, *Chem. Ber.* **94**, 968 (1961).

¹³³ H. Brandl, H. Kaiser, H. Richert, and F. Rozanski, German Patent 1,945,209 (1971) [CA 74, P141733 (1971)].

¹³⁴ Japanese Patent 70 29,809 (1970) [CA 74, 31564 (1971)].

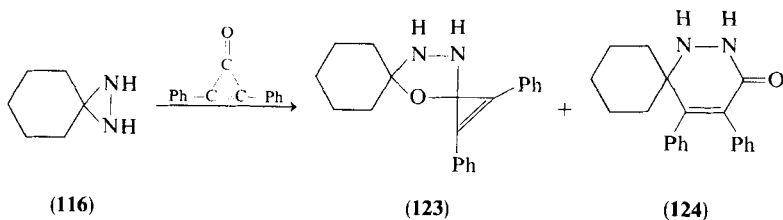
¹³⁵ M. Otsuka, S. Yukimura, H. Yamaguchi, and T. Kawasaki, Japanese Patent 70 05,544 (1970) [CA 72, 111106 (1970)].

¹³⁶ H. W. Heine and L. Heitz, *J. Org. Chem.* **39**, 3192 (1974).

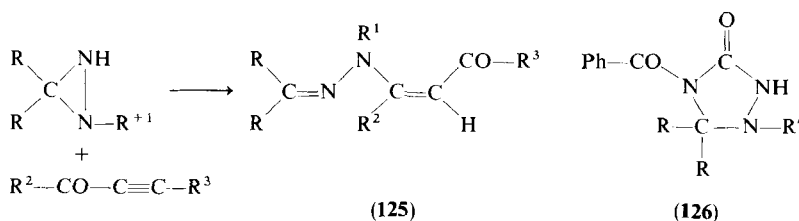
¹³⁷ H. W. Heine, R. Henrie, L. Heitz, and S. R. Koovali, *J. Org. Chem.* **39**, 3187 (1974).

¹³⁸ J. W. Lown, *J. Chem. Soc. C*, 1338 (1969).

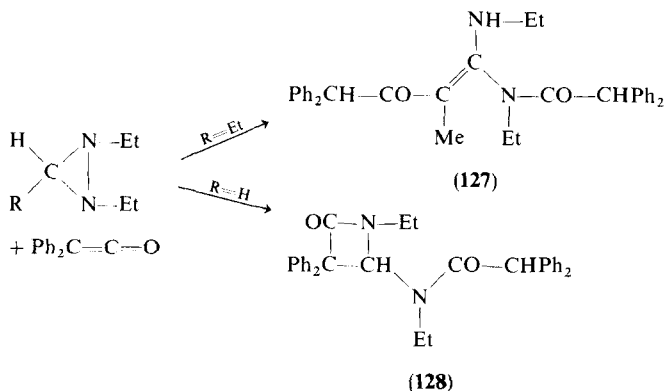
¹³⁹ E. V. Dehmlow and J. Schoenefeld, *Z. Naturforsch., Teil B* **30**, 824 (1975).



Alkynyl ketones react to form ene-hydrazones **125**^{140,141}; benzoyl isocyanate forms the semicarbazide derivative **126**.¹⁴²



By reaction with diphenyl ketene, the N—N bond of the diaziridine is broken. Depending on the substituents at the ring carbon either the ketene aminal **127** or the azetidine **128** is obtained.^{142,143}



Two-electron oxidation of the NH-group of a diaziridine results in ring opening opposite to the H-bearing nitrogen and formation of **129**, which

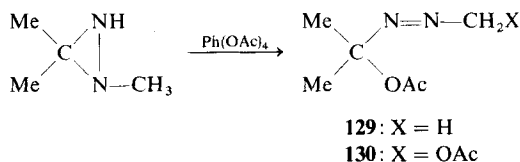
¹⁴⁰ H. W. Heine, T. R. Hoye, P. G. Williard, and R. C. Hoye, *J. Org. Chem.* **38**, 2984 (1973).

¹⁴¹ T. K. Klindukhova and V. N. Yandovskii, *Zh. Org. Khim.* **10**, 877 (1974).

¹⁴² M. Komatsu, N. Nishikaze, M. Sakamoto, Y. Ohshiro, and T. Agawa, *J. Org. Chem.* **39**, 3198 (1972).

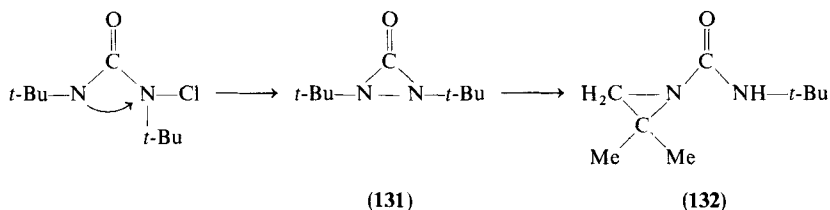
¹⁴³ T. Agawa, Y. Ohshiro, M. Komatsu, and N. Nishikaze, Japanese Patent 7 51 17,765 (1975) [*CA* **84**, 59159 (1976)].

bears some resemblance to the decomposition of *N*-chloroaziridines. The main product of the reaction (**130**) is the result of subsequent acetoxylation.¹⁴⁴



C. DIAZIRIDINONES AND DIAZIRIDINIMINES

The first diaziridinone was prepared by Greene and Stowell.^{145,146} By the action of strong bases on *N*-chloro-*N,N'*-di-*t*-butylurea, the unexpectedly stable 1,2-di-*t*-butyldiaziridinone **131** was formed. Obviously, ring-opening reactions are hindered by bulky groups without comparable hindrance of the ring-forming reaction.



Even at 175°C **131** decomposes only slowly, potassium *t*-butoxide opens the ring only on heating for some hours in *t*-butanol. HCl in pentane, however, leads to fast ring opening. Reduction leads to the starting urea.

A curious isomerization was observed on action of hydrazines on **131**. In competition with the reduction, aziridine **132** is formed, probably by a radical-chain mechanism.¹⁴⁷

The first diaziridinimines were obtained analogously some years later by Quast and Schmitt.¹⁴⁸ For example, tri-*t*-butylguanidine was *N*-chlorinated and cyclized to **133** by strong bases. The imine **133** is less stable than the analogous diaziridinone. It decomposes at 150°C, giving azoalkane and isocyanide.

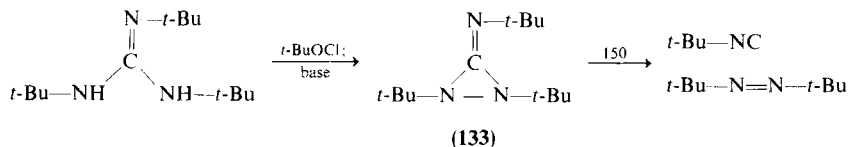
¹⁴⁴ V. N. Yandovskii and P. M. Adrov, *Zh. Org. Khim.* **10**, 2235 (1974).

¹⁴⁵ F. D. Greene and J. C. Stowell, *J. Am. Chem. Soc.* **86**, 3569 (1964).

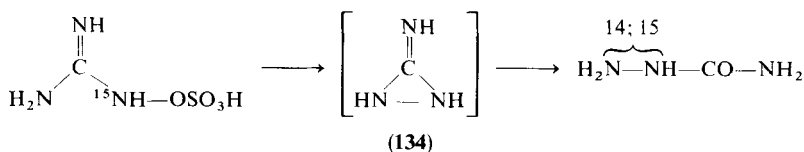
¹⁴⁶ F. D. Greene, J. C. Stowell, and W. R. Bergmark, *J. Org. Chem.* **34**, 2254 (1969).

¹⁴⁷ F. D. Greene, W. R. Bergmark, and J. G. Pacifici, *J. Org. Chem.* **34**, 2263 (1969).

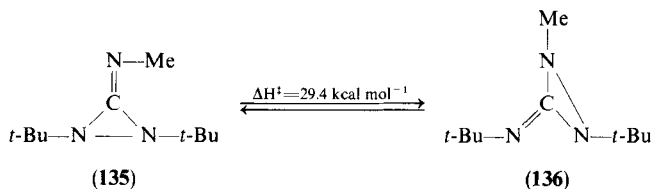
¹⁴⁸ H. Quast and E. Schmitt, *Angew. Chem., Int. Ed. Engl.* **8**, 448 (1969).



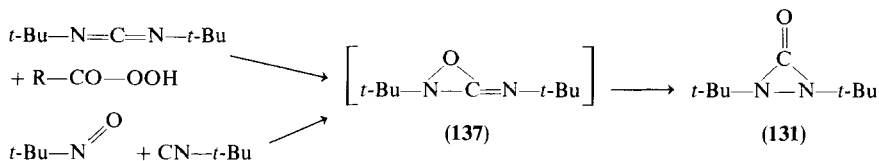
Formation of diaziridinimine **134** had been postulated shortly before to account for a labeling experiment: Ohme and Preuschhof¹⁴⁹ had found that in the transformation of hydroxyguanidine-*O*-sulfonic acid to semicarbazide there is equilibration of the ¹⁵N-content between hydroxylamine nitrogen and one other nitrogen.



An interesting rearrangement is observed at temperatures as low as 60–90°C. The compounds are converted into isomeric diaziridinimines by N—N cleavage and recyclization.¹⁵⁰ Both **135** and **136** form a mixture of both compounds, **135** being somewhat more stable. This rearrangement is analogous to the valence isomerization of methylenecyclopropane.



Valence isomerizations of heteroanalogs of methylenecyclopropanes permit interesting access into the series of diaziridinones. Reactions of either di-*t*-butyl carbodiimide with a peracid or of nitrosoisobutane with *t*-butyl isocyanide, undertaken to make the oxaziridinimine **137**, led to diaziridinone **131**, probably by valence isomerization of the originally formed **137**.^{151,152}

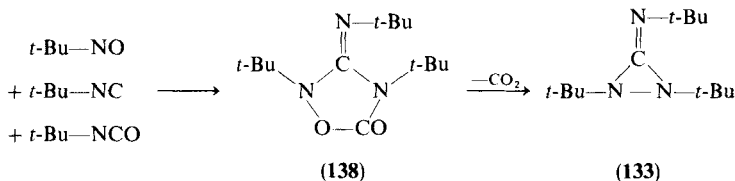


¹⁴⁹ R. Ohme and H. Preuschhof, *Justus Liebigs Ann. Chem.* **721**, 25 (1969).

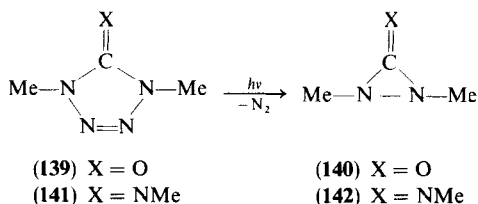
¹⁵⁰ H. Quast and E. Schmitt, *Chem. Ber.* **103**, 1234 (1970).

¹⁵¹ F. D. Greene, W. R. Bergmark, and J. F. Pazos, *J. Org. Chem.* **35**, 2813 (1970).

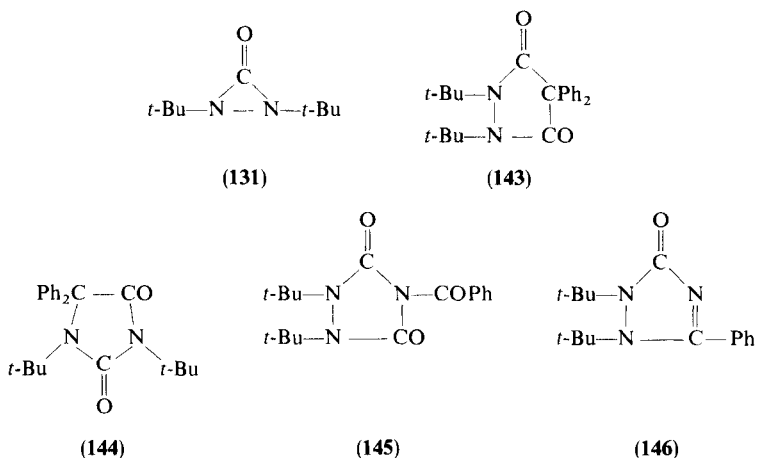
During experiments to trap a reaction product of a nitroso compound and isonitrile with an alkyl isocyanate, an additional way of formation of diaziridinimines was discovered. Besides some other heterocycles the five-membered ring compound **138** was formed, which yielded **133** by extrusion of carbon dioxide at 150°. ¹⁵³



Recently Quast reported some photochemical preparations of diaziridinones and diaziridinimines. The three-membered ring compounds **140** and **142** are formed by nitrogen extrusion from the tetrazolines **139** and **141**, respectively. ¹⁵⁴



Ohshiro and co-workers ¹⁵⁵ included diaziridinones into their investigations on reactions of three-membered rings with heterocumulenes. With



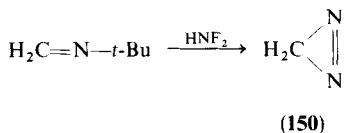
¹⁵² F. D. Greene and J. F. Pazos, *J. Org. Chem.* **34**, 2269 (1969).

¹⁵³ C. J. Wilkerson and F. D. Greene, *J. Org. Chem.* **40**, 3112 (1975).

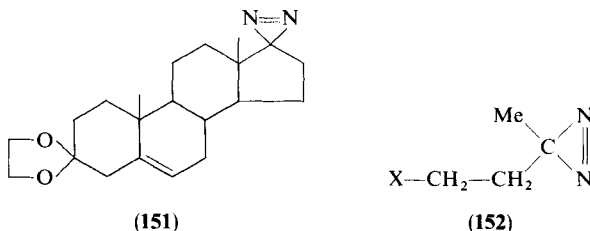
¹⁵⁴ H. Quast and L. Bieber, *Angew. Chem.* **87**, 422 (1975).

¹⁵⁵ Y. Ohshiro, M. Komatsu, Y. Yamamoto, K. Takaki, and T. Agawa, *Chem. Lett.*, 383 (1974).

Synthesis of the parent compound **150**, "cyclodiazomethane," from Schiff bases of formaldehyde and difluoroamine, also proceeds with dealkylation.¹⁶²



The search for biologically active diazirines again confirmed the broad applicability of diazirine synthesis. Since the tendency to diaziridine formation parallels the tendency to acetalization,¹⁶³ three-membered ring formation is impeded by steric hindrance, by conjugation of the carbonyl group with unsaturated groups, as well as by strongly electron-withdrawing groups. Thus diaziridine and diazirine formation proceeded especially smoothly in the 3-position of steroids, less smoothly in the 2-position and only in exceptional cases in the 17-position, for example, with formation of **151**.¹⁶⁴



The synthetic activity in the steroid field was followed by extensive investigations on diazirine synthesis in other classes of compounds. For example, diazirines of type **152** were prepared, where X stands for the hydroxy group,¹⁶⁵ a carboxyl group or derivatives of it,^{165,166} amino groups,¹⁶⁶ acetal groups,¹⁶⁵ or heterocycles^{167,168} (**152a-e**).

Further diazirines were prepared by transformations of functional groups, leaving the diazirine group intact. Esterifications, and cleavage of esters and acetals, could be carried out as well as transformation of carboxyl groups to acid chlorides and Hofmann elimination of a quaternary ammonium group. There was a report on the oxidation of hydroxyl groups

¹⁶² W. H. Graham, *J. Am. Chem. Soc.* **88**, 4677 (1966).

¹⁶³ E. Schmitz, see Schmitz,² p. 80.

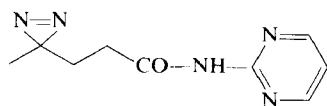
¹⁶⁴ Novo Therapeutisk Laboratorium, Netherlands Patent 6,505,966 (1966) [*CA* **66**, 115864 (1967)].

¹⁶⁵ R. F. R. Church and M. J. Weiss, U.S. Patent 3,525,736 (1970) [*CA* **73**, 109777 (1970)].

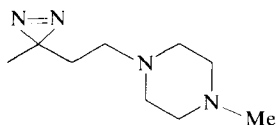
¹⁶⁶ R. F. R. Church and M. J. Weiss, U.S. Patent 3,509,131 (1970) [*CA* **73**, 25431 (1970)].

¹⁶⁷ R. F. R. Church and M. J. Weiss, U.S. Patent 3,459,752 (1969) [*CA* **71**, 112968 (1969)].

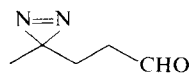
¹⁶⁸ R. F. R. Church, R. D. Maleike, and M. J. Weiss, *J. Med. Chem.* **15**, 514 (1972).



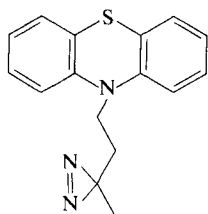
(152a)



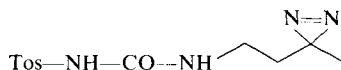
(152b)



(152c)



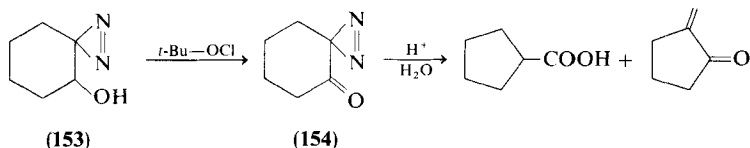
(152d)



(152e)

to keto groups in steroids without affecting the diazirine group. Even reactions with diborane,¹⁵⁷ and the addition of chlorine¹⁰⁹ and ozone¹⁶⁹ to a double bond were carried out without destruction of the diazirine group.

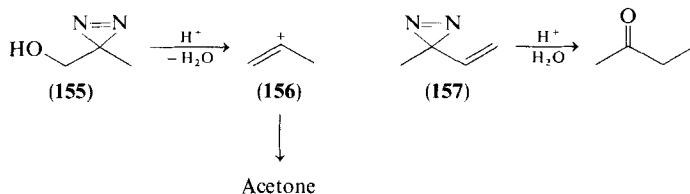
Whereas the diazirine group survives almost all chemical operations going on at suitable distances from it, it is very sensitive to all operations producing a partial positive charge at a carbon atom adjacent to the three-membered ring. The oxidation of α -hydroxydiazirines, e.g., **153**, succeeds only under very mild conditions and leads to ketones very sensitive toward acids.¹⁷⁰ Dilute acid transforms **154** at room temperature with nitrogen elimination to a mixture of cyclopentane carboxylic acid and methylene-cyclopentanone.



(153)

(154)

When the α -hydroxydiazirine **155** is treated with acid, breaking of the C—O bond results in elimination of nitrogen. Acetone is formed, probably



(155)

(156)

(157)

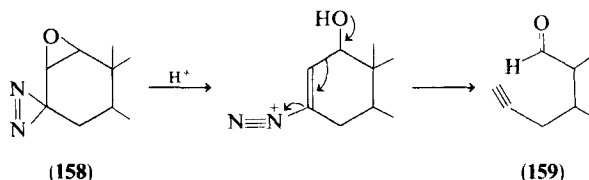
Acetone

¹⁶⁹ E. Schmitz and C. Hörig, *Chem. Ber.* **100**, 2101 (1967).

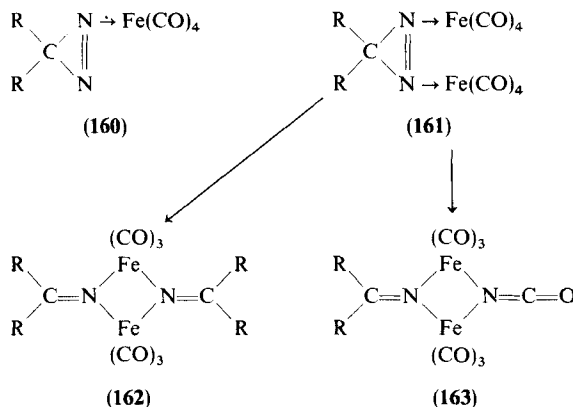
¹⁷⁰ E. Schmitz, C. Hörig, and C. Gründemann, *Chem. Ber.* **100**, 2093 (1967).

by addition of water to the unsaturated cation **156**. The α,β -unsaturated diazine **157** yields butanone under the action of aqueous acid.¹⁷⁰

The acid-catalyzed opening of an epoxide ring can also give rise to a positive charge at a carbon atom adjacent to the three-membered ring. With certain steroid diazirines **158**, nitrogen evolution occurs with opening of a carbocyclic ring to give alkynylaldehydes **159**.¹⁷¹



A novel field was opened by Albine and Kisch¹⁷² and by Volpin and co-workers¹⁷³ by allowing diazirines to react with metal carbonyls. 3,3-Dimethyl and 3,3-pentamethylenediazirine react with $Fe_2(CO)_9$ to form the iron tetracarbonyl derivatives **160** and **161**. In acid solution **161** is slowly converted into **162** and **163**.



B. DIAZIRINE-DIAZOALKANE INTERCONVERSION

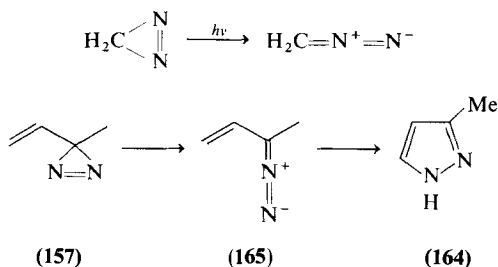
When first prepared in 1960, the thermal stability of diazirines was astonishing. Although they are more energy-rich than their linear isomers by ca. 30 kcal mol⁻¹, they are decomposed only at temperatures above

¹⁷¹ P. Borrevang, J. Hjort, R. T. Rapala, and R. Edie, *Tetrahedron Lett.*, 4905 (1968).

¹⁷² A. Albine and H. Kisch, *J. Organomet. Chem.* **94**, 75 (1975).

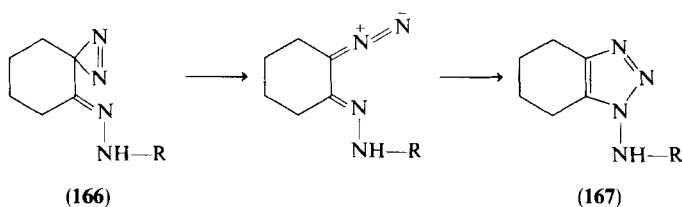
¹⁷³ I. A. Tichanova, K. Jähnisch, V. G. Andrianov, S. F. Bjalozkii, Yu. T. Strutschov, V. G. Shur, E. Schmitz, and M. E. Volpin, *Koord. Khim.* **2**, 1653 (1976).

100°C with activation energies higher than 30 kcal. We now know that both the linear-cheletropic cleavage to nitrogen and carbene and the isomerization to linear diazo compounds are symmetry-forbidden processes.¹⁷⁴ The prediction that photoconversion of a diazirine to a diazoalkane should be an allowed process, and that participation of an additional pair of electrons should allow thermal ring opening of a diazirine, were observed beforehand. As early as 1964 the photorearrangement of diazirine to diazo-methane was reported,¹⁷⁵ followed by a report on thermal rearrangement of methylvinyl diazirine **157** to 3-methylpyrazole **164**.¹⁷⁰ The latter reaction starts with opening of the diazirine to the isomeric diazo compound **165**.^{174,176}



The intermediacy of **165** was easily established, since diazirines are very stable toward acids, whereas diazoalkanes transform carboxylic acids into esters. A carboxylic acid added to rearranging **157** was converted into its butenoate.

A thermal ring opening of diazirines to diazoalkanes was also discussed for the hydrazones **166** of α -ketodiazirines,¹⁷⁴ their attempted preparation being followed by ring enlargement to aminotriazoles **167**.¹⁷⁷



There is also a report on the photocyclization of diazo compounds to diazirines. Diazoacetic acid piperidide **168** is converted into the isomeric

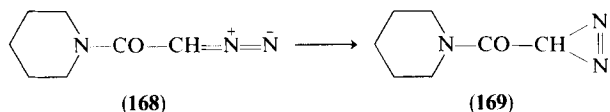
¹⁷⁴ E. Schmitz, *Pure Appl. Chem. Suppl.*, 283 (1971).

¹⁷⁵ M. J. Amrich and J. A. Bell, *J. Am. Chem. Soc.* **86**, 292 (1964).

¹⁷⁶ M. T. H. Liu and K. Toriyama, *Can. J. Chem.* **51**, 2393 (1973).

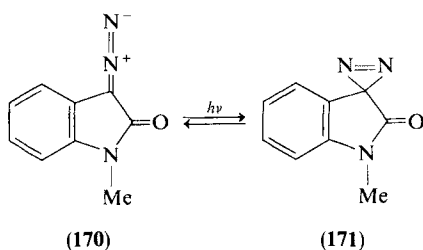
¹⁷⁷ E. Schmitz, A. Stark, and C. Hörig, *Chem. Ber.* **98**, 2509 (1965).

diazirine **169** even by visible light; the same is observed with diazoacetyl derivatives of proline benzyl ester and phenylalanine benzyl ester.¹⁷⁸



This reaction is reversible. By irradiating with light of the wavelength absorbed by the diazirine, the linear isomers are recovered.¹⁷⁹

On illumination an equilibrium between the phenoldiazonium betaine **170** and the isomeric diazirine **171** is reached, containing ca. 15% of the diazirine.¹⁸⁰



C. THERMAL AND PHOTOLYTIC DECOMPOSITION OF DIAZIRINES

Diazirines were detected when there was broad activity in the carbene field. From their structure, cleavage to nitrogen and carbene was foreseeable, and this was shown to occur on photolysis¹⁸¹ as well as on thermolysis.¹⁸² As early as 1962, Frey and Stevens in a series of papers reported on photolysis of simple diazirines.¹⁸³ According to these authors, diazirines are especially fit for the study of excited intermediates and their stabilization products. Products of isomerization of carbenes, i.e., olefins and cyclopropanes, are formed containing more energy than is necessary for their further decomposition. Their stabilization by loss of energy to partners competes with stabilization by subsequent reactions.

Thermolysis of diazirines also leads to carbenes. In contrast to decomposition reactions of linear diazo compounds, there is no problem of dis-

¹⁷⁸ G. Lowe and J. Parker, *J. Chem. Soc. D*, 1135 (1971).

¹⁷⁹ R. A. Franich, G. Lowe, and J. Parker, *J.C.S. Perkin I*, 2036 (1972).

¹⁸⁰ E. Voigt and H. Meier, *Chem. Ber.* **108**, 3326 (1975).

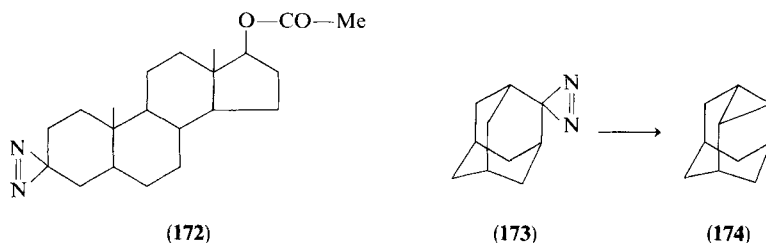
¹⁸¹ H. M. Frey and I. D. R. Stevens, *Pure Appl. Chem.* **9**, 527 (1964).

¹⁸² For review, Schmitz,² p. 147.

¹⁸³ H. M. Frey and I. D. R. Stevens, *Proc. Chem. Soc.* 79 (1962).

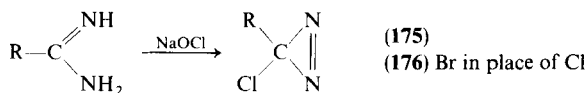
crimination between true carbene reactions and reactions via "carbenoids." In the majority of cases diazirines are easier to obtain, easier to isolate, and—taking into account some tendency to explode—easier to decompose under definite conditions than their linear isomers. So there was never any doubt about the carbene character of their cleavage products.

So far, however, the attractive potentialities of diazirines to act as carbene precursors have not been exploited to the full. In the steroid field, ketones have been transformed to olefins via diazirines¹⁰⁹; **172** yielded the Δ^2 -compound preferentially. Pyrolysis of spirodiazirine **173** at 320°C yielded 96% dehydroadamantane **174**.¹⁸⁴



Diazirine was used as the carbene precursor in an experiment to make diazomethane from methylene and nitrogen in the gas phase. As shown by means of labeled nitrogen, there was 4% diazomethane formation.¹⁸⁵

During the past 10 years thermal as well as photochemical decomposition of 3-chloro- and 3-bromodiazirine has been investigated in detail. Compounds **175** and **176** as well as analogous compounds are easily obtained by reaction of amidines with hypohalites according to Graham.¹⁸⁶



Phenylchlorodiazirine is more sensitive to shock than nitroglycerol.¹⁸⁷ Explosions during work with methylchlorodiazirine were reported.¹⁸⁸

Kinetic investigations on simple alkylchlorodiazirines were carried out by Frey and co-workers.¹⁸⁹ According to them, methylchlorodiazirine de-

¹⁸⁴ S. D. Isajev, A. G. Jurtschenko, F. N. Stepanow, G. G. Koljada, and S. S. Novikov, *Zh. Org. Khim.* **9**, 430 (1973).

¹⁸⁵ E. A. Shilov, A. A. Shteinman, and M. J. Tjabin, *Tetrahedron Lett.*, 4177 (1968).

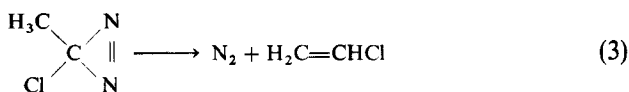
¹⁸⁶ W. H. Graham, *J. Am. Chem. Soc.* **87**, 4396 (1965).

¹⁸⁷ J. J. Wheeler, *Chem. Eng. News* **48**, 10 (20.7./1970).

¹⁸⁸ M. T. H. Liu, *Chem. Eng. News* **52**, 3 (g.g./1974).

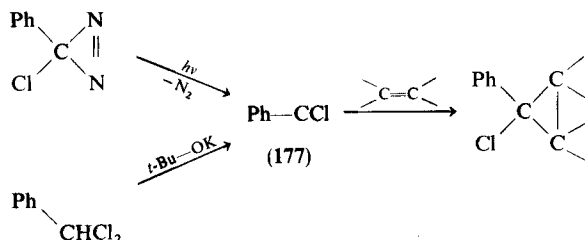
¹⁸⁹ M. R. Bridge, H. M. Frey, and M. T. H. Liu, *J. Chem. Soc. A*, 91 (1969); H. M. Frey and M. T. H. Liu, *J. Chem. Soc. A*, 1916 (1970).

composes thermally following first-order kinetics with formation of nitrogen and vinyl chloride [Eq. (3)].



The ethyl, propyl, isopropyl, and *t*-butyl compounds also yield products easy to rationalize as products of stabilization of primarily formed carbenes.

Comparison of reactions of halocarbenes, which were produced from either alkylhalodiazirines by nitrogen extrusion, or by the usual method of eliminating hydrogen halide from dihaloalkanes by means of strong bases, bears special interest. Thus phenylchlorocarbene **177** was produced both from benzyldiene chloride by potassium-*t*-butoxide, and by photolysis of phenylchlorodiazirine.¹⁹⁰ Competition experiments with mixtures of olefins showed rate differences, especially remarkable for the isobutene-tetramethylethylene pair. The rate proportion was 0.20 when the diazirine



was used as carbene precursor, 0.38 in the case of benzyldiene chloride. Similar results were obtained with phenylbromocarbene.¹⁹¹ The hypothesis that phenylbromocarbene prepared from benzyldiene bromide exists as a KBr-complex was demonstrated convincingly. Experiments in the presence of a crown ether, which complexed the alkali, revealed identical selectivities for both types of carbene.¹⁹²

Extensive investigations by Liu confirmed a first-order reaction of thermal decomposition of chlorodiazirines as well as formation of typical stabilization products of carbenes. Thus tetrachloroethylene was formed from trichloromethylchlorodiazirine **178**¹⁹³; norcaranes were obtained on decomposition of arylchlorodiazirines in cyclohexene; from cyclooctylchloro-

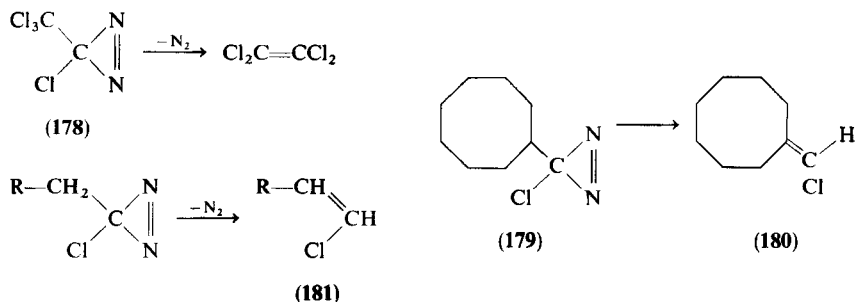
¹⁹⁰ R. A. Moss, J. R. Whittle, and P. Freidenreich, *J. Org. Chem.* **34**, 2220 (1969).

¹⁹¹ R. A. Moss, *Tetrahedron Lett.*, 4905 (1967).

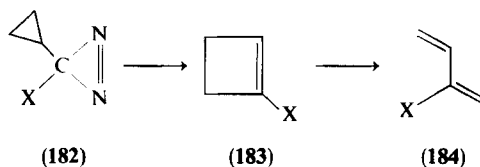
¹⁹² R. A. Moss and F. G. Pilkievicz, *J. Am. Chem. Soc.* **96**, 5632 (1974).

¹⁹³ M. T. H. Liu and K. Toriyama, *Int. J. Chem. Kinet.*, 229 (1972).

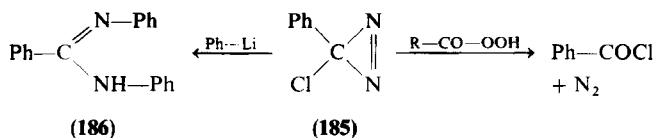
diazirine **179**, the corresponding olefin **180** was formed by intramolecular stabilization of a chlorocarbene.¹⁹⁴ There was only poor influence of either substituents or solvents,¹⁹⁵ but there was some preference of *cis*-olefin formation in nonpolar solvents.¹⁹⁶



Cyclopropylchlorodiazirine as well as the analogous bromo compound **182** decompose thermally to vibrationally excited 1-halocyclobutenes **183**, which either isomerize to 2-halo-1,3-butadienes **184**, or lose their energy by collisions.¹⁹⁷



Two cleavage reactions of phenylchlorodiazirine **185** were described: action of phenyllithium to **185** led to diphenylbenzamidine **186**,¹⁹⁸ and *m*-chloroperbenzoic acid produced benzoyl chloride and nitrogen.¹⁹⁹



¹⁹⁴ M. T. H. Liu and D. H. T. Chien, *J.C.S. Perkin II*, 937 (1974).

¹⁹⁵ M. T. H. Liu and K. Toriyama, *Can. J. Chem.* **50**, 3009 (1972).

¹⁹⁶ M. T. H. Liu and D. H. T. Chien, *Can. J. Chem.* **52**, 246 (1974).

¹⁹⁷ W. J. Engelbrecht and S. W. J. Van der Merwe, *J. S. Afr. Chem. Inst.* **28**, 148 (1975).

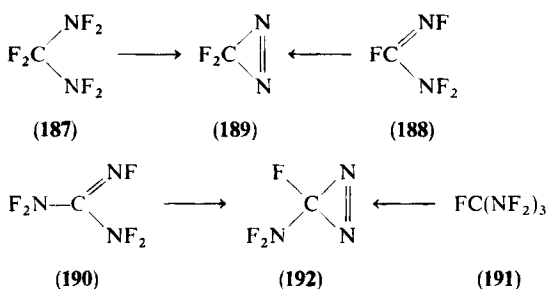
¹⁹⁸ A. Padwa and D. Eastman, *J. Org. Chem.* **34**, 2728 (1969).

¹⁹⁹ M. T. H. Liu and J. C. W. Li, *Tetrahedron Lett.*, 1329 (1974).

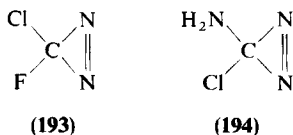
D. FLUORODIAZIRINES

Diazirines fluorinated at the ring carbon were first described by Mitsch,²⁰⁰ and shortly afterward by Rebertus and co-workers.²⁰¹ They are obtained from suitable perfluorinated amines by reduction with ferrocene²⁰² or iodide,²⁰¹ as well as by reduction with diphenylamine,²⁰³ semicarbazide hydrochloride²⁰⁴ and by electrolytic reduction.²⁰³

For example, both the ferrocene method of Mitsch and the iodide method of Rebertus yield difluorodiazirine **189** from either perfluoroformamidine **188** or perfluoro-methylenediamine **187**. Both methods likewise allowed the preparation of difluoroaminofluorodiazirine **192** from perfluoroguanidine **190** and from perfluorotriaminomethane **191**.



By use of chlorine-containing starting materials as well as by working in the presence of chloride, diazirines **193**²⁰¹ or **194**²⁰⁴ could be obtained.



The formation of a fluorodiazirine was also observed by Stevens and Graham from the action of methoxide on the fluorinated lactam **195**.²⁰⁵

The isomerization of difluorocyanamide to difluorodiazirine on contact with cesium fluoride has been described.²⁰⁶

²⁰⁰ R. A. Mitsch, *J. Heterocycl. Chem.* **1**, 59 (1964).

²⁰¹ R. L. Rebertus, J. J. McBrady, and J. G. Gagnon, *J. Org. Chem.* **32**, 1944 (1967).

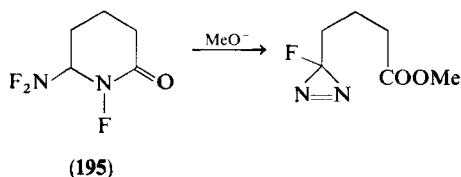
²⁰² R. A. Mitsch, *J. Heterocycl. Chem.* **3**, 245 (1966).

²⁰³ R. L. Rebertus and P. E. Toren, *J. Org. Chem.* **32**, 4045 (1967).

²⁰⁴ J. L. Zollinger, C. D. Wright, J. J. McBrady, D. H. Dybvig, F. A. Fleming, G. A. Kurhajec, R. A. Mitsch, and E. W. Neuvar, *J. Org. Chem.* **38**, 1065 (1973).

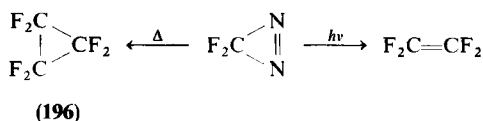
²⁰⁵ T. E. Stevens and W. H. Graham, *J. Am. Chem. Soc.* **89**, 182 (1967).

²⁰⁶ M. D. Meyers and S. Frank, *Inorg. Chem.* **5**, 1455 (1966).



Syntheses of these fluorodiazirines were published only after publication on their decomposition reactions.^{200,207-211} As expected, thermal as well as photochemical decomposition led to the corresponding fluorocarbenes. Typical carbene reactions, such as cyclopropanation of added olefins and formation of substituted ethylenes in the absence of reaction partners, were observed.

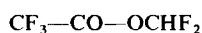
For example, perfluorocyclopropane **196** was formed on thermolysis of difluorodiazirine. Photolysis yielded tetrafluoroethylene.



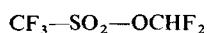
Cyclopropanations of suitable olefins proceed stereospecifically,²⁰⁷ so formation of singlet difluorocarbene is plausible as an intermediate in both thermolysis and photolysis.²⁰⁸

The production of difluorocarbene from a chemically inert precursor allowed a study of carbene reactions with reactive partners like chlorine, iodine, and nitrogen dioxide. Thus, difluorodihalomethanes were obtained with halogens; NO₂ showed only modest reactivity to form difluorodinitromethane, tetrafluoroethylene being formed as a by-product.²⁰⁹

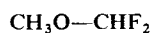
Carboxylic acids, sulfonic acids, and alcohols could also be used as substrates of difluorocarbene reactions, yielding compounds **197**, **198**, and **199**.²¹⁰



(197)



(198)



(199)

Diazirine **192** loses nitrogen even at 75°. ²¹¹ Cyclopropanation with added olefin must compete with intramolecular stabilization of the carbene **200** to imine **201**.

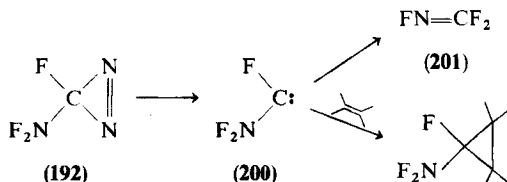
²⁰⁷ R. A. Mitsch, *J. Heterocycl. Chem.* **1**, 271 (1964).

²⁰⁸ R. A. Mitsch, *J. Am. Chem. Soc.* **87**, 758 (1965).

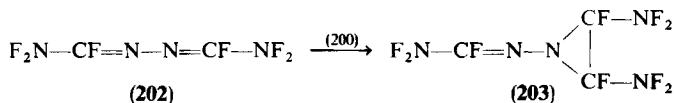
²⁰⁹ R. A. Mitsch, *J. Heterocycl. Chem.* **1**, 233 (1964).

²¹⁰ R. A. Mitsch and J. E. Robertson, *J. Heterocycl. Chem.* **2**, 152 (1965).

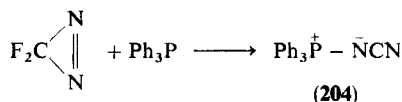
²¹¹ R. A. Mitsch, E. W. Neuvar, R. J. Koshar, and D. H. Dybvig, *J. Heterocycl. Chem.* **2**, 371 (1965).



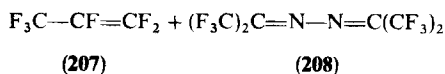
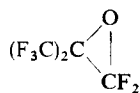
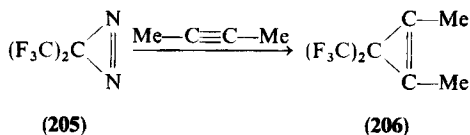
Further reaction between carbene **200** and diazine **192** leads to azine **202**, which takes up more carbene to give the aziridine **203**.²¹²



Phosphorus(III) compounds react with difluorodiazirine with N-N cleavage and formation of **204**.²¹³



Novel ways of formation^{201,214} as well as observations on chemical behavior of bistrifluoromethylidiazirine **205** have been reported, **205** itself being known since 1965.²¹⁵



In the absence of partners, there is formation of olefin **207** and azine **208**; dimethylacetylene is transformed into the cyclopropene **206**; carbonyl fluoride yields the epoxide **209**.

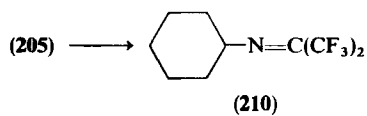
²¹² R. A. Mitsch, E. W. Neuvar, and P. H. Ogden, *J. Heterocycl. Chem.* **4**, 389 (1967).

²¹³ R. A. Mitsch, *J. Am. Chem. Soc.* **89**, 6297 (1967).

²¹⁴ D. M. Gale, W. J. Middleton, and C. G. Krespan, *Abstr. Pap., Am. Chem. Soc., 151st Meet.*, 1966.

²¹⁵ R. B. Minasyan, E. M. Rokhlin, N. P. Gambaryan, Y. V. Zeifman, and I. L. Knunyants, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 761 (1965).

A product (**210**) of the reaction with cyclohexane has incorporated only one N-atom.²¹⁶



²¹⁶ W. J. Middleton, D. M. Gale, and C. G. Krespan, *J. Am. Chem. Soc.* **90**, 6813 (1968).

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Selenium–Nitrogen Heterocycles

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I. Introduction

In the book “Organic Selenium Compounds; Their Chemistry and Biology,” edited by Klayman and Gunther, several chapters have been devoted to the review of selenium heterocycles including one chapter on

selenium heterocycles by Bulka.¹ In that article the literature is very comprehensively reviewed until 1970. Since that time a large number of papers have appeared concerning the preparation, properties, and reactions of selenium–nitrogen heterocycles.

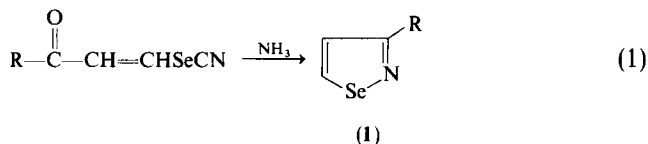
In the present review an attempt is made to cover the literature through 1976 with some later references. In order to create a historical overlap, in some cases reference is made to material already covered by Bulka.

II. Five-Membered Selenium–Nitrogen Heterocycles

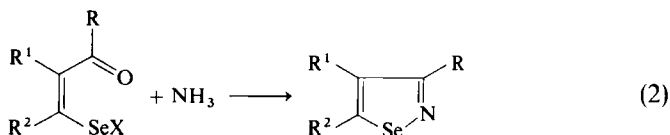
A. FIVE-MEMBERED SELENIUM HETEROCYCLES WITH ONE NITROGEN ATOM

1. 1,2-Selenazoles (*Isoselenazoles*)

Very few syntheses of isoselenazoles are reported. The parent compound and its 3-methyl derivative (**1**) were prepared by Wille *et al.*² by ring closure of 3-selenocyanatoacrolein and the corresponding butenone in liquid ammonia [Eq. (1)].



Using the basic features of this reaction shown in Eq. (2), other derivatives of the ring system have been prepared:

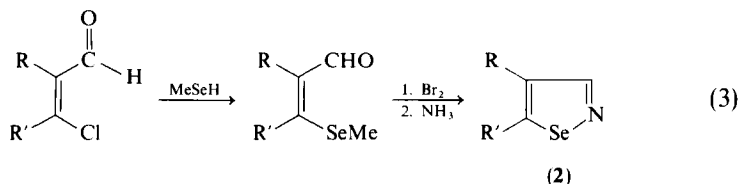


Recently Weber and Renson³ reported that the reaction of β -chloro- α,β -disubstituted crotonaldehyde with methylselenomercaptan gave β -methylseleno- α,β -disubstituted crotonaldehydes, which were subsequently cyclized with bromine and ammonia to give the isoselenazoles (**2**). [Eq. (3)].

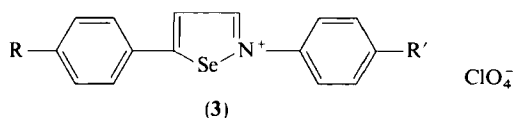
¹ E. Bulka, in "Organic Selenium Compounds; Their Chemistry and Biology" (D. L. Klayman and W. H. H. Gunther, eds.), p. 459. Wiley (Interscience), New York, 1973.

² F. Wille, A. Ascherl, G. Kaupp, and C. Capeller, *Angew. Chem.* **74**, 753 (1962).

³ R. Weber and M. Renson, *J. Heterocycl. Chem.* **10**, 267 (1973).

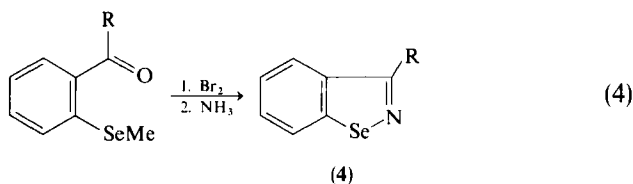


Several isoselenazolium perchlorates (3) were prepared by Liebscher and Hartmann⁴ by treating 4-RC₆H₄CCl=CHCH=NMe₂⁺ ClO₄⁻ with NaSeCN and 4-R'C₆H₄NH₂.

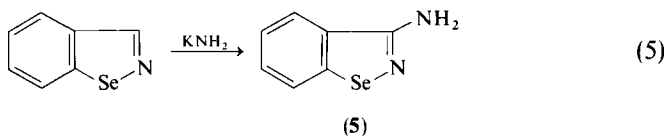


2. 1,2-Benzisoselenazoles

Using the same method of ring closure described above, Weber and Renson³ were able to prepare a number of 1,2-benzisoselenazoles. Thus, the derivatives (4) were prepared through the reaction of *o*-MeSeC₆H₄COR with bromine followed by ammonia [Eq. (4)]



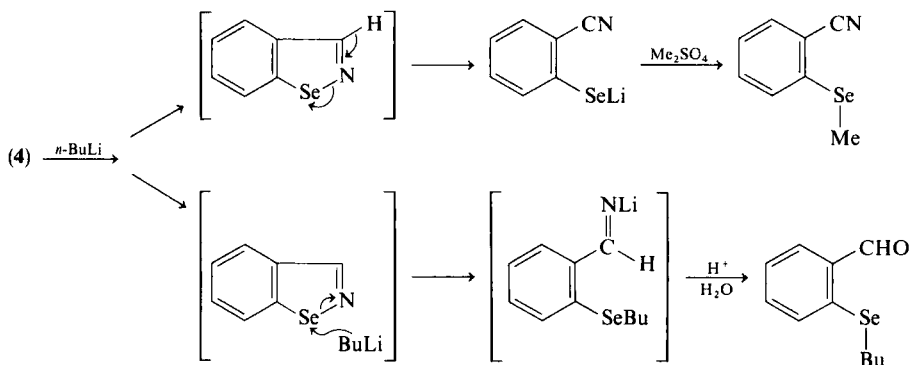
These authors studied the action of several electrophilic and nucleophilic reagents on unsubstituted 1,2-benzisoselenazole and found that while electrophiles attack the benzene ring, nucleophiles either substitute the 3-position of the heterocycle or cleave the ring. Thus nitration and bromination led to the formation of monosubstituted derivatives at the 5 and 7 position. Potassium amide, however, gave the 3-amino derivative (5)⁵ [Eq. (5)].



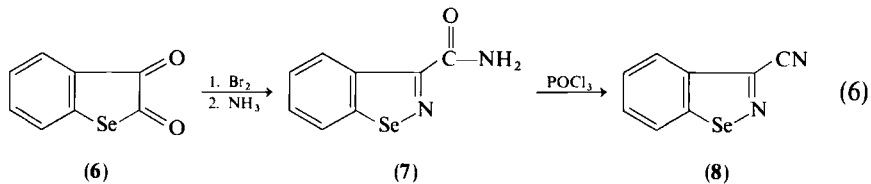
⁴ J. Liebscher and H. Hartmann, *Synthesis* **4**, 273 (1976).

⁵ R. Weber and M. Renson, *J. Heterocycl. Chem.* **12**, 1091 (1975).

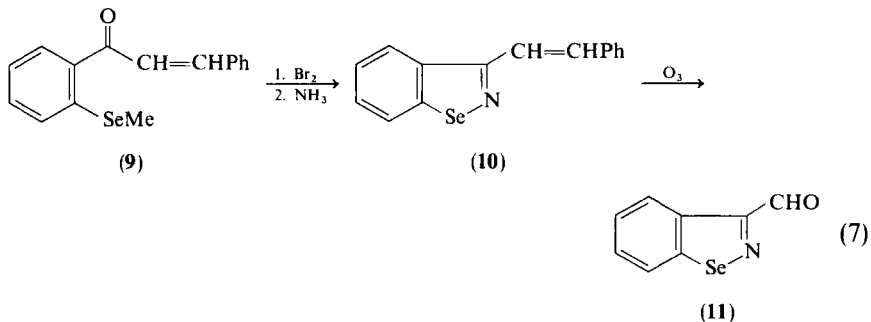
On the other hand, metallation results in ring opening, and, depending on reaction conditions (temperature and solvent), the two different products shown in Scheme 1 result.⁵

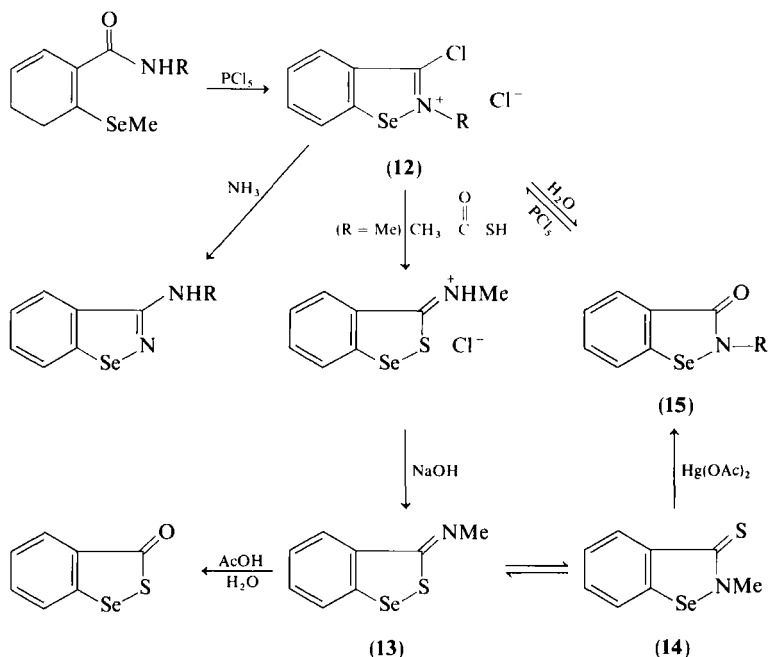


3-Substituted-1,2-benziselenazoles were also prepared by Weber and Renson⁵ by the reaction of selenonaphthenequinone (6) with bromine followed by ammonia. Subsequent reaction of the intermediate amide (7) with POCl_3 gave the 3-cyano derivative 8. [Eq. (6)].



Similarly, *o*-methylselenobenzalacetophenone (9) was cyclized to give the 3-styrylbenzisoselenazole (10), which on ozonization gave the 3-formyl derivative (11).⁵ [Eq. (7)].





SCHEME 2

Weber and Renson⁶ have also prepared the 1,2-benzisoselenazolium salts **12** by ring closure of N-substituted *o*-methylselenobenzamide with phosphorus pentachloride. The 1,2-benzisoselenazolium salt was further converted into the other heterocycles shown in Scheme 2.

In the above sequence of reactions, it is interesting to note that, whereas 1,2-benzisoselenazolone (**15**) is quite stable, the 1,2-benzisoselenazothione (**14**) is unstable and in polar medium is in equilibrium with the imine (**13**).

3. 1,3-Selenazoles

The classical method of forming 1,3-selenazole derivatives involves a modification of the Hantzsch thiazole synthesis. For this purpose derivatives of selenocarboxamides, in place of thioamides, are allowed to react with α -halocarbonyl compounds **16** to give the corresponding 1,3-selenazoles (**17**).⁷⁻¹⁰ [Eq. (8)].

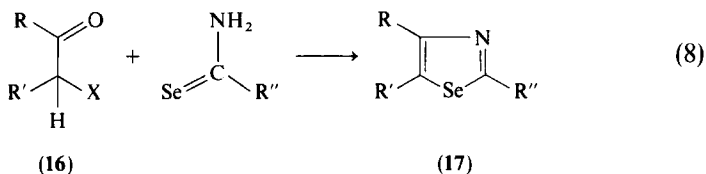
⁶ R. Weber and M. Renson, *Bull. Soc. Chim. Fr.*, 1124 (1976).

⁷ G. Hofmann, *Justus Liebigs Ann. Chem.* **250**, 294 (1889).

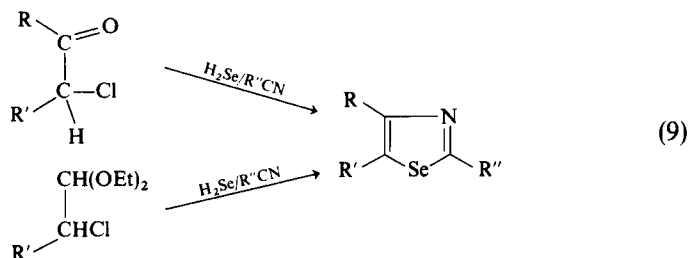
⁸ L. G. S. Brooker, G. H. Keyes, and F. L. White, *J. Am. Chem. Soc.* **57**, 2492 (1935).

⁹ P. Chauvin, J. Morel, C. Paulmier, and P. Pastour, *C. R. Acad. Sci., Ser. C* **274**, 1347 (1972).

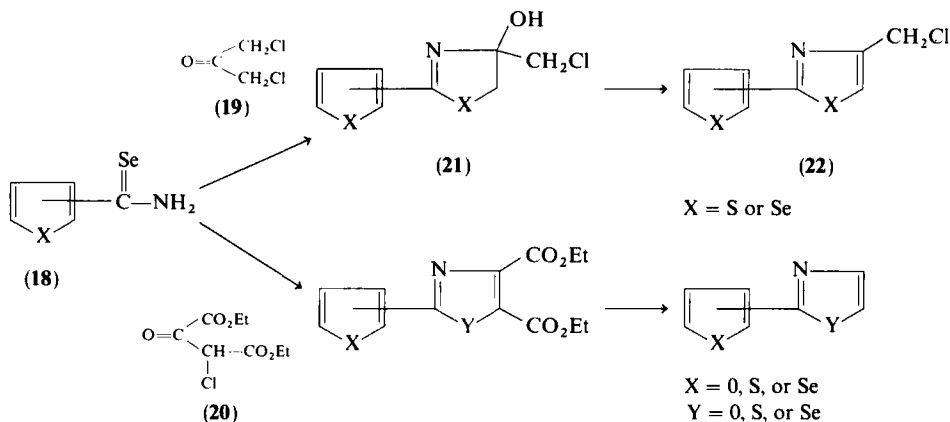
¹⁰ P. Chauvin, J. Morel, and P. Pastour, *C. R. Acad. Sci., Ser. C* **276**, 1453 (1973).



The above reaction was first reported by Hofmann.⁷ It permits the synthesis of a wide variety of compounds. By the use of suitable reaction partners, the selenocarboxamide as well as α -halocarbonyl components could be varied. The difficulty encountered in the synthesis of alkylselenocarboxamides could be overcome by passing hydrogen selenide into a mixture of a nitrile and α -haloketone or 2-haloaldehyde acetal in the presence of condensation catalysts.¹¹ [Eq. (9)]. Selenourea forms 2-aminoselenazoles.¹²



Several 2-(2- or 3-furyl, thienyl, and selenophene-yl)selenazoles have been obtained by the reaction of the appropriate selenoamide (18) and α -haloketone (19 or 20)¹³ (Scheme 3).



SCHEME 3

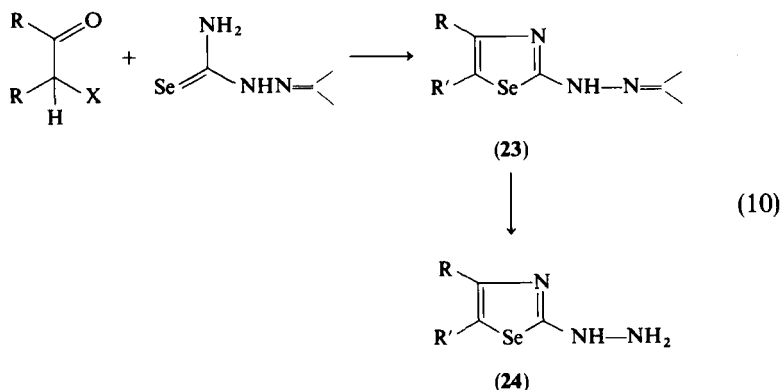
¹¹ J. Haginiwa, *Yakugaku Zasshi* **68**, 191 (1948) [*CA* **47**, 8074 (1953)].

¹² J. Metzger and P. Baily, *C. R. Acad. Sci.* **237**, 906 (1953).

¹³ P. Chauvin, J. Morel, P. Pastour, and J. Martinez, *Bull. Soc. Chim. Fr.*, 2079 (1974).

The selenazoline **21** was the initial product of the reaction of **18** with **19**. It was smoothly dehydrated to the selenazole (**22**) in acetic acid.

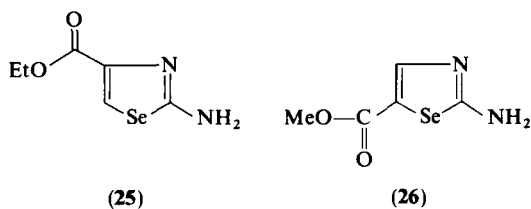
2-Selenazolyhydrazines (**24**) were obtained by the reaction of a selenosemicarbazone with α -haloketones and subsequent hydrolysis of the intermediate hydrazones (**23**).¹⁴ [Eq. 10].



The selenosemicarbazones needed for these reactions were obtained from acetoneazine and hydrogen selenocyanate.¹⁵

2-Amino derivatives of selenazoles are generally prepared from the haloketone or aldehyde and selenoureas. The latter can easily be obtained by either passing H_2Se through a solution of cyanamide or a carbodiimide¹⁶ or from acyl selenoureas, which are obtained from the corresponding acyl halide and potassium selenocyanate.¹⁷

The reactions of selenourea with ethyl bromopyruvate and methyl formylchloroacetate gave 2-amino-4-carbethoxyselenazole (**25**) and 2-amino-5-carbomethoxyselenazole (**26**), respectively.¹⁸



Selenazoles of type **27** have been formed in high yield by condensing the acylselenourea PhCONHCHSeNMePh with α -haloketones.¹⁹ As shown in

¹⁴ E. Bulka, *Chem. Scr.* **8A**, 39 (1975).

¹⁵ R. Huls and M. Renson, *Bull. Soc. Chim. Belg.* **65**, 511 (1956).

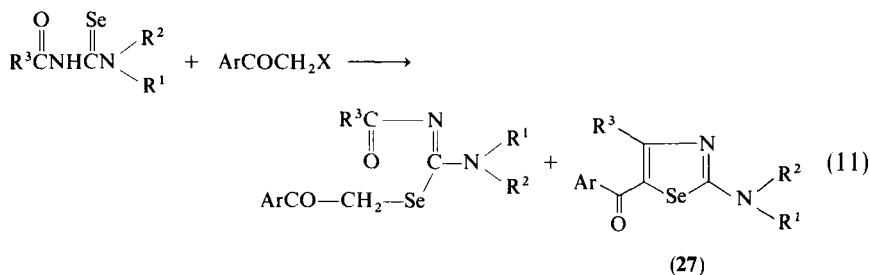
¹⁶ R. E. Dunbar and E. P. Painter, *J. Am. Chem. Soc.* **69**, 1833 (1947).

¹⁷ E. Bulka, K. D. Ehlers, and E. Tucek, *Z. Chem.* **10**, 404 (1970).

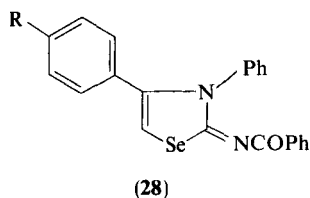
¹⁸ A. Shafiee and I. Lalezari, *J. Heterocycl. Chem.* **12**, 675 (1975).

¹⁹ J. Liebscher and H. Hartmann, *Z. Chem.* **16**, 18 (1976).

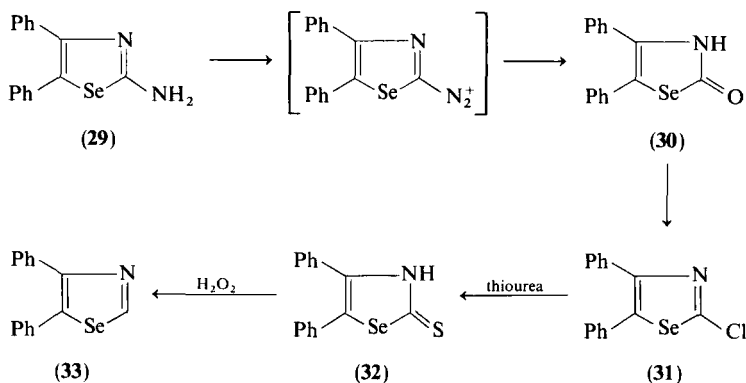
Eq. (11), the selenazole (**27**) is not formed by the same mechanism as the usual Hantzsch-type reaction.



Interestingly, if the selenourea derivative used is PhCONHCSeNHPh , the N-substituted selenazole **28** is obtained by the usual Hantzsch reaction.¹⁹

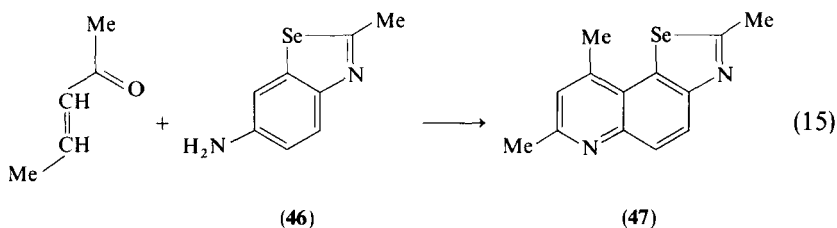


Bulka, who undertook a systematic study of the reactivity of the various positions of the selenazole ring, attempted to synthesize this ring by degradation of 2-substituted selenazoles. Thus diazotization of 2-amino-4,5-diphenylselenazole (**29**) followed by hydrolysis afforded 4,5-diphenyl-2-selenazolone (**30**). Phosphorus oxychloride reacted with the latter compound to give the 2-chloro derivative (**31**), which after treatment with thiourea gave the 2-thione (**32**). The last upon oxidation with H_2O_2 gave the desired 2-unsubstituted selenazole (**33**) in low overall yield¹⁴ (Scheme 4).

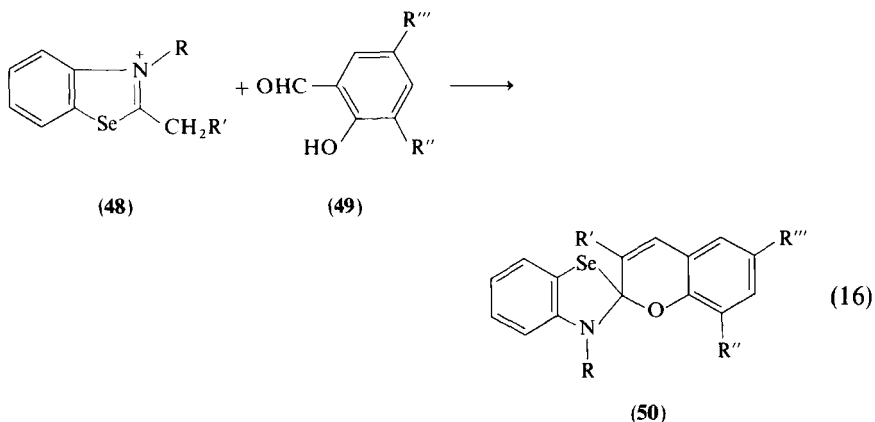


SCHEME 4

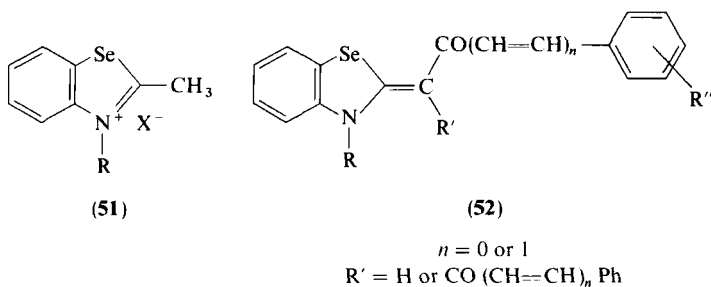
The reaction of 6-amino-2-methylbenzoselenazole (46) with 3-penten-2-one gave, via a simple Doebner–Miller type of reaction, the trimethyl substituted selenazoloquinoline 47.²⁵ [Eq. (15)].



The 2-alkylbenzoselenazolium salt 48 reacted with substituted *o*-hydroxybenzaldehydes (49) to give the spiro compound 50.²⁶ [Eq. (16)].



Condensation of the quaternary salt 51 with substituted benzoyl or cinnamoyl chlorides gave mono- and diacylmethylene derivatives 52.²⁷

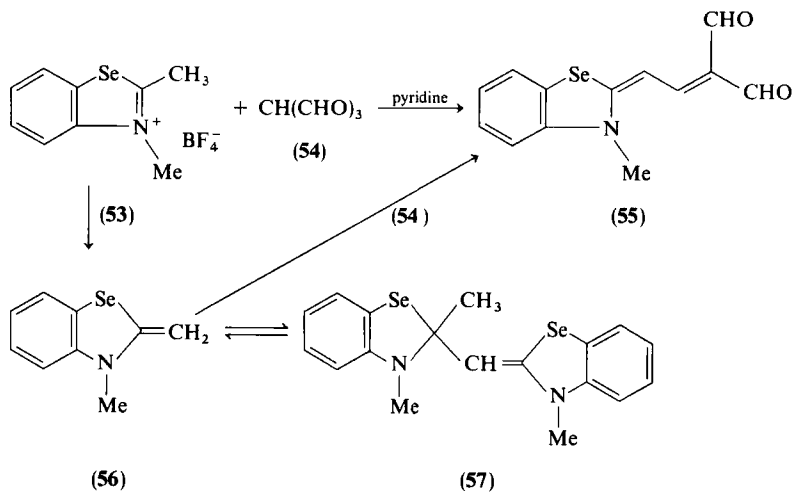


²⁵ E. Barni and G. Di Modica, *J. Heterocycl. Chem.* **8**, 693 (1971).

²⁶ R. Guglielmetti, E. Davin-Pretelli, and J. Metzger, *Bull. Soc. Chim. Fr.*, 556 (1971).

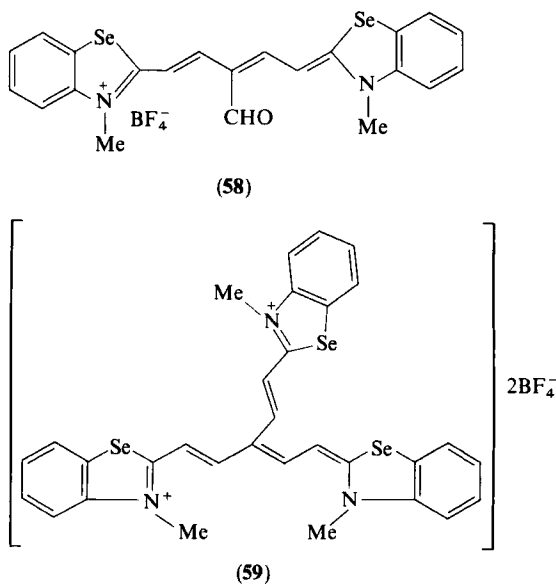
²⁷ A. Mistr, V. Laznicka, and B. Simak, *Collect. Czech. Chem. Commun.* **38**, 3616 (1973).

2,3-Dimethylbenzoselenazolium fluoroborate (**53**) reacted with 1 mol of triformylmethane (**54**) to give the γ -formyltetramethinemercyanine **55**. The latter could also be prepared from the base **56**, which is in equilibrium with its dimer **57**²⁸ (Scheme 6).



SCHEME 6

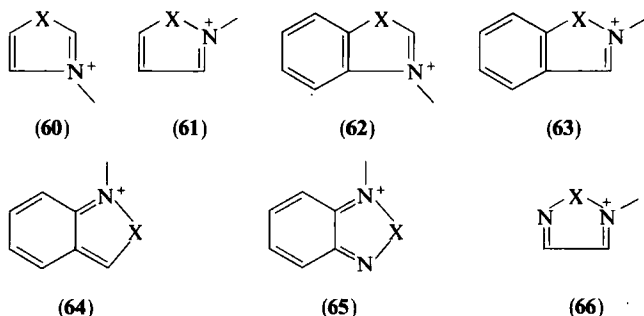
When the benzoselenazolium salt is in excess, the di- and tri-condensation products (**58** and **59**) result.



²⁸ C. Reichardt and W. Mormann, *Chem. Ber.* **105**, 1815 (1972).

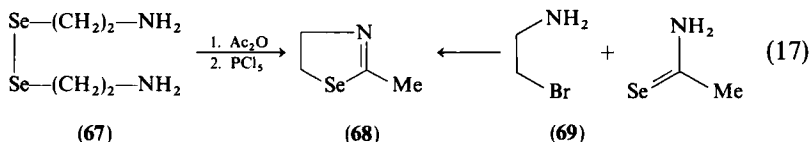
The NMR and UV spectra of the above compounds were examined and interpreted with respect to π -electron density and ($N-V_1$) transition energies obtained by Hückel molecular orbital (HMO) calculation.²⁹ Carbon-13 NMR spectra of 2-methylbenzoselenazolium salts were reported by Kleinpeter and Borsdorf.³⁰ A linear chemical shift–electron density relation was obtained. The shift of the C-2 atom is reported to be a good indication of the acidities.

The *N*-methyl chemical shifts in quaternized azoles, isoazoles, diazoles, and their benzologs (**60**–**66**) were reported by Davis and co-workers.³¹ The shifts appear to be determined by resonance from the heteroatom, decreasing in the order of the donating ability of the heteroatom: $NMe > O > S \sim Se$. In the 1,2 orientation, the electronegativity effects were also important, as evidenced by a general downfield shift; the order of donation is $NMe > S \sim Se > O$.



5. Selenazolines and Selenazolidines

In 1892, Michels³² reported the synthesis of 2-methylselenazoline (**68**) through the reaction of bis(2-aminoethyl)diselenide (**67**) with acetic anhydride followed by ring closure with phosphorus pentachloride. The same selenazoline was also prepared from 2-bromoethylamine(hydrochloride) (**69**) and selenoacetamide³³ [Eq. (17)].



²⁹ E. Kleinpeter, R. Borsdorf, G. Bach, and J. Von Grossmann, *J. Prakt. Chem.* **315**, 587 (1973).

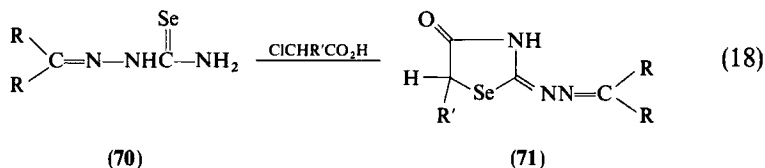
³⁰ E. Kleinpeter and R. Borsdorf, *J. Prakt. Chem.* **315**, 765 (1973).

³¹ M. Davis, L. W. Deady, and E. Homfeld, *J. Heterocycl. Chem.* **11**, 1011 (1974).

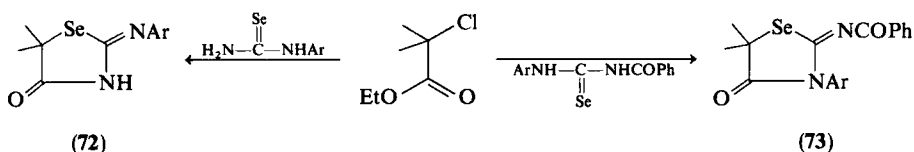
³² W. Michels, *Chem. Ber.* **25**, 3048 (1892).

³³ British Patent 392,410 (1932) [*Chem. Zentralbl.* II, 1934 (1933)].

Comrie *et al.*³⁴ prepared a number of 2,4-dioxoselenazolidine 2-alkylidenehydrazones (**71**) by the reaction of α -halocarboxylic acids with ketone and aldehyde selenosemicarbazones (**70**), [Eq. (18)], and Tsurkan *et al.*³⁵ have recently made other derivatives of **71** by a similar method.

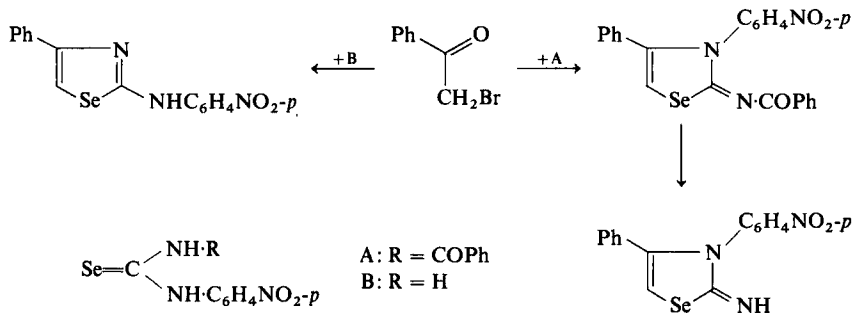


It is interesting that in this and in the following selenazoline preparations, starting with unsymmetrical ureas, only one of the two possible isomeric products is produced. Thus, Bulka describes the reaction of monosubstituted or unsymmetrically 1,3-disubstituted selenoureas with α -haloesters to provide only the 2-arylimino derivatives of 4-oxoselenazolidine (**72**) and 2-benzoylimino-3-aryl-4-oxoselenazolidine (**73**), respectively,¹⁴ (Scheme 7).



SCHEME 7

This selectivity is discussed in terms of the reduced nucleophilicity of the acylated amino group, compared with the other nitrogen atom of the selenourea. In support, the different products obtained from the two reactions of Scheme 8 are cited.¹⁴

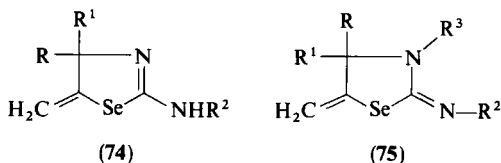


SCHEME 8

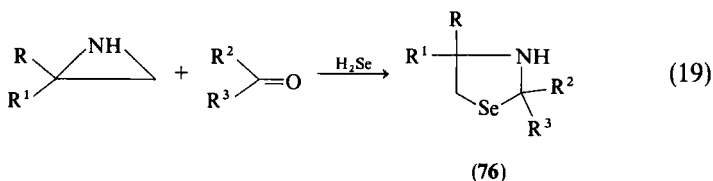
³⁴ A. M. Comrie, D. Dingwall, and J. B. Stenlake, *J. Chem. Soc.*, 5713 (1963).

³⁵ A. A. Tsurkan, V. V. Groshev, V. I. Efremenko, and E. N. Troshenko, *Farm. Zh. (Kiev)* **27**, 69 (1972) [*CA* **78**, 720139 (1973)].

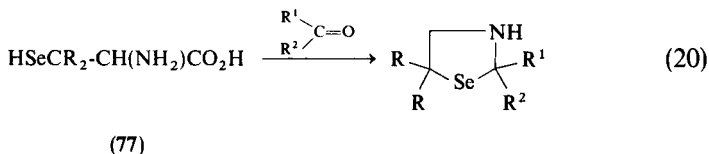
Selenazolines and selenazolidines of type (74) and (75) were prepared by condensing the corresponding benzyl or aryl isoselenocyanates with appropriate aminoacetylenes $RR^1C(NHR^3)C\equiv CH$.³⁶



A different series of selenazolidines (76) has been prepared by Draguet and Renson³⁷ by the treatment of hydrogen selenide with aziridines and aldehydes or ketones [Eq. (19)].

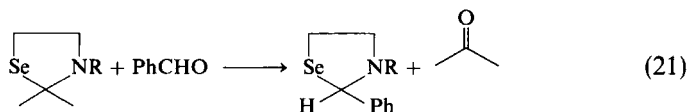


Using selenopenicillamines (77) instead of the aziridines, other selenazolidine derivatives were obtained.³⁸ [Eq. (20)].



R = H or Me

The selenazolidine ring is quite labile. Draguet and Renson³⁹ studied some of its reactions and reported that it undergoes a facile ring-open chain tautomerism as shown by its reaction with aldehydes [Eq. (21)].



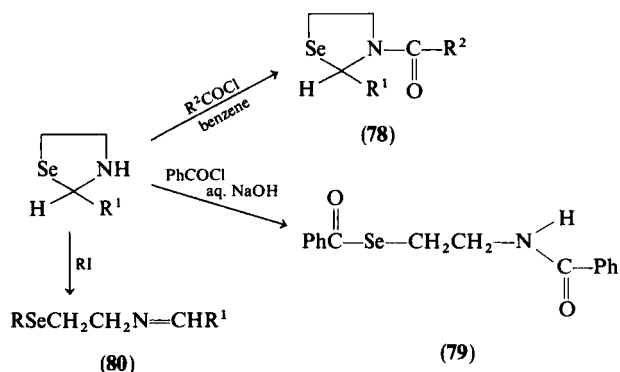
³⁶ I. N. Azerbaev, L. A. Tsoi, and A. B. Asmanova, USSR Patent 351,857 (1972) [CA 78, 43484 (1973)].

³⁷ C. Draguet and M. Renson, *Bull. Soc. Chim. Belg.* **75**, 243 (1966); **81**, 279, 295 (1972).

³⁸ C. Draguet and M. Renson, *Bull. Soc. Chim. Belg.* **81**, 303 (1972).

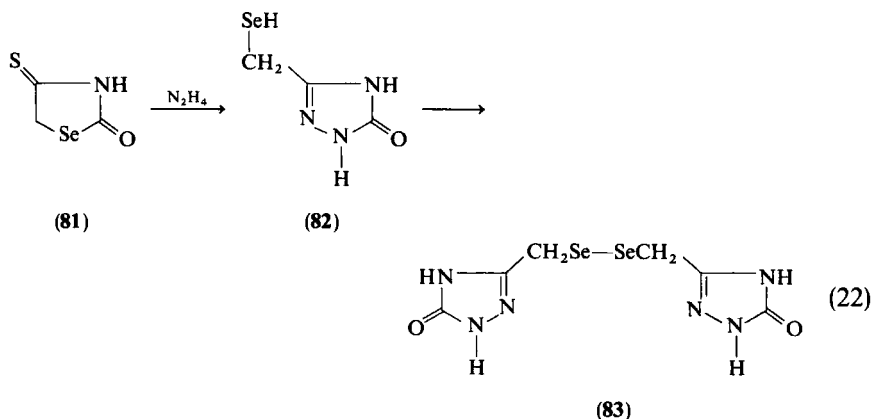
³⁹ C. Draguet and M. Renson, *Bull. Soc. Chim. Belg.* **81**, 289 (1972).

The lability of the ring is further evident in some of the alkylation and acylation reactions studied by the above authors. Thus, while acylation of selenazolidines in inert solvents gave the *N*-acyl compound **78**, acylation in aqueous alkali resulted in the ring-opened product **79**. Similarly, alkylation with methyl and *n*-butyl iodide opened the ring, and compound **80** was formed. Such cleavage on alkylation is not seen in the analogous thiazolidines (Scheme 9).



SCHEME 9

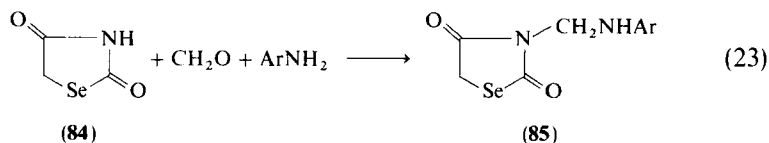
Ring opening has also been observed with 4-thiono-2-selenazolidone (**81**) upon treatment with hydrazine. The product triazolinone (**82**) oxidized to the diselenide (**83**)⁴⁰ [Eq. (22)].



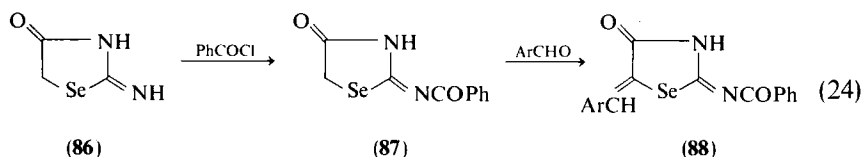
In contrast to the lability of the ring in **81**, no reactions leading to ring opening of 2,4-selenazolidinedione (**84**) has been reported. Indeed, the latter

⁴⁰ O. P. Shvaika, V. N. Artemov, V. E. Kononenko, and S. N. Baranov, *Khim. Geterotsikl. Soedin.*, 930 (1973) [*CA* **79**, 115502 (1973)].

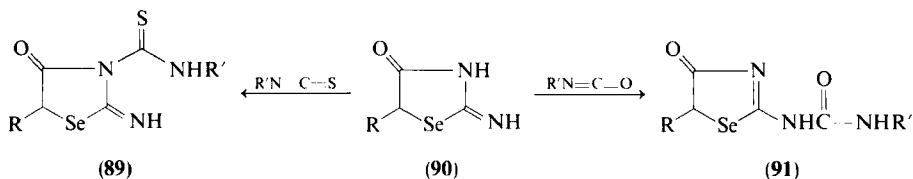
compound smoothly reacts with arylamines and formaldehyde to give a Mannich product (**85**)⁴¹ [Eq. (23)].



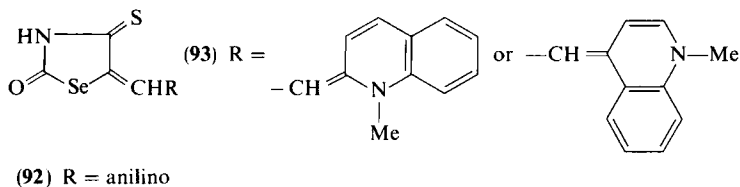
2-Imino-4-selenazolidinone (**86**) could be acylated by benzoyl chloride; the product (**87**) condensed with arylaldehydes to give **88**⁴² [Eq. (24)].



5-Alkyl-2-imino-4-selenazolidinone (**90**) with isothiocyanates gave thioureas of type **89**. Isocyanates, however, added to the imino nitrogen to give ureas of type **91**⁴³ (Scheme 10).



The 4- thiono-2-selenazolidone dyes (**93**) were obtained by the treatment of compound **92** with an appropriate lepidinium or quinaldinium derivative.⁴⁴



⁴¹ V. E. Kononenko, B. E. Zhitar, and S. N. Baranov, *Zh. Org. Khim.* **9**, 61 (1973) [*CA* **78**, 84308 (1973)].

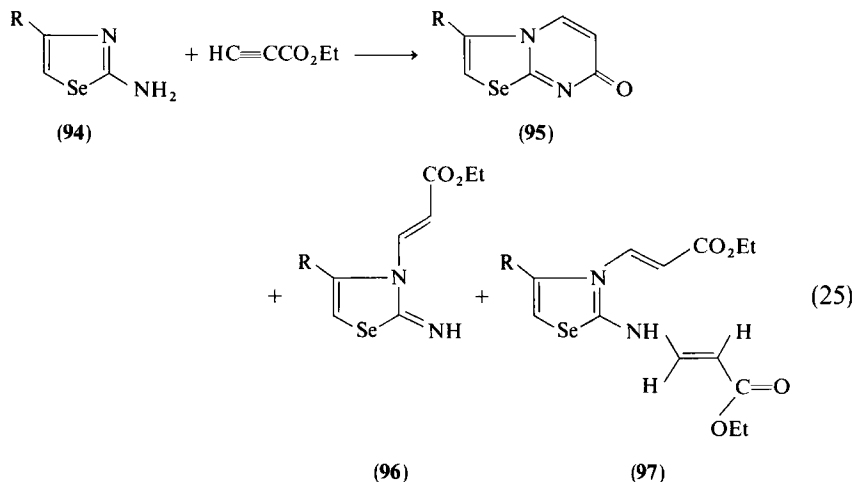
⁴² A. A. Tsurkan and V. V. Groshev, *Farm. Zh. (Kiev)* **28**, 82 (1973) [*CA* **78**, 159525 (1973)].

⁴³ H. Siaglo, S. Andrzejewski, E. Kleczek, and D. Prelicz, *Pol. J. Pharmacol. Pharm.* **27**, 57 (1975) [*CA* **83**, 79157 (1975)].

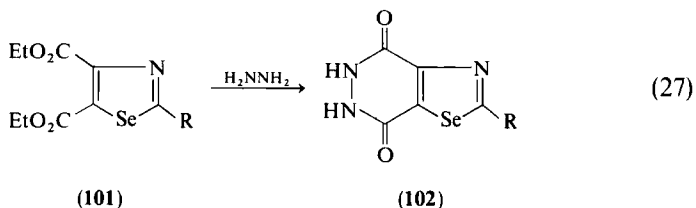
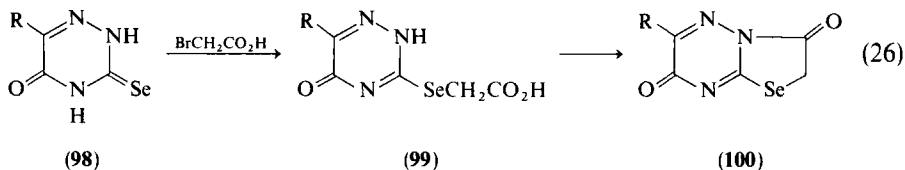
⁴⁴ V. E. Kononenko, B. E. Zhitar, and S. N. Baranov, *Khim. Geterotsikl. Soedin.*, 1493 (1973) [*CA* **80**, 82817 (1974)].

6. Condensed Selenazoles and Selenazolidines

The reaction of 2-aminoselenazoles (**94**) with ethyl propiolate was studied by Shafiee and Lalezari.⁴⁵ In this reaction, in addition to 7*H*-selenazolo-[3,2-*a*]pyrimidin-7-ones (**95**), adducts **96** and **97** were formed. Compound **95** is probably formed through ring closure of the *cis*-isomer of **96** [Eq. (25)].



Representatives (**100**) of the selenazolo[3,2-*b*][1,2,4]triazine system are accessible from 6-substituted 2,3,4,5-tetrahydro-*as*-triazin-5-one-3-selenone (**98**) by reaction with bromoacetic acid and ring closure of the intermediate products (**99**) with acetic anhydride⁴⁶ [Eq. (26)].

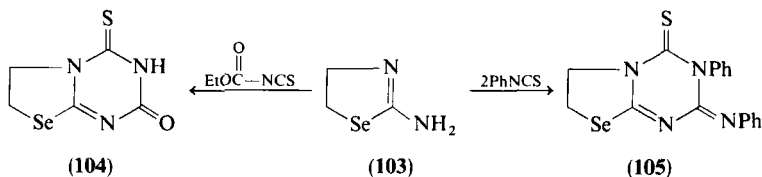


⁴⁵ A. Shafiee and I. Lalezari, *J. Heterocycl. Chem.* **12**, 675 (1975).

⁴⁶ A. Shafiee and I. Lalezari, *J. Heterocycl. Chem.* **8**, 1011 (1971).

Substituted selenazolo[4,5-*d*]pyridazine-4,5-diones (**102**) were obtained by heating the diester **101** with hydrazine⁴⁷ [Eq. (27)].

The reaction of 2-amino-2-selenazoline (**103**) with carboethoxy isothiocyanate gave 2,3,6,7-tetrahydro-4*H*-selenazolo[3,2-*a*]-s-triazin-2-one-4-thione (**104**).⁴⁸ A similar reaction of phenylisothiocyanate with **103** had been reported to give the triazine derivative **105**⁴⁹ (Scheme 11).



SCHEME 11

B. FIVE-MEMBERED SELENIUM HETEROCYCLES WITH TWO NITROGEN ATOMS

1. 1,2,3-Selenadiazoles

The 1,2,3-selenadiazoles without fused rings were unknown until 1969 when Lalezari *et al.*^{50,51} described the synthesis of 4-aryl-1,2,3-selenadiazoles (**106**) by the selenium dioxide oxidative ring closure of the semicarbazones of acetophenones. The mechanism proposed for this reaction is shown in Scheme 12. The mechanism was verified by the isolation of diphenylurea from the oxidation of the 4-phenylsemicarbazone derivative. The alternative mechanism proposed by Meier and Voigt does not account for this finding.⁵²

Using the appropriate ketone semicarbazones, several 4-substituted and 4,5-disubstituted 1,2,3-selenadiazoles were prepared by this method. Unsubstituted and 5-substituted rings were obtained by the reaction of the corresponding aldehydes.⁵³ Ketones possessing two different α -methylene or methyl groups give a mixture of the two isomeric 1,2,3-selenadiazoles **107** and **108** [Eq. (28)].

The dominant product is **107** in accordance with the carbanion stability of the α -carbon atoms. Similarly, 3-phenyl-2-propanone semicarbazone

⁴⁷ P. Chauvin, J. Morel, P. Pastour, and J. Martinez, *Bull. Soc. Chim. Fr.*, 2099 (1974).

⁴⁸ D. L. Klayman and T. S. Wood, *J. Org. Chem.* **39**, 1819 (1974).

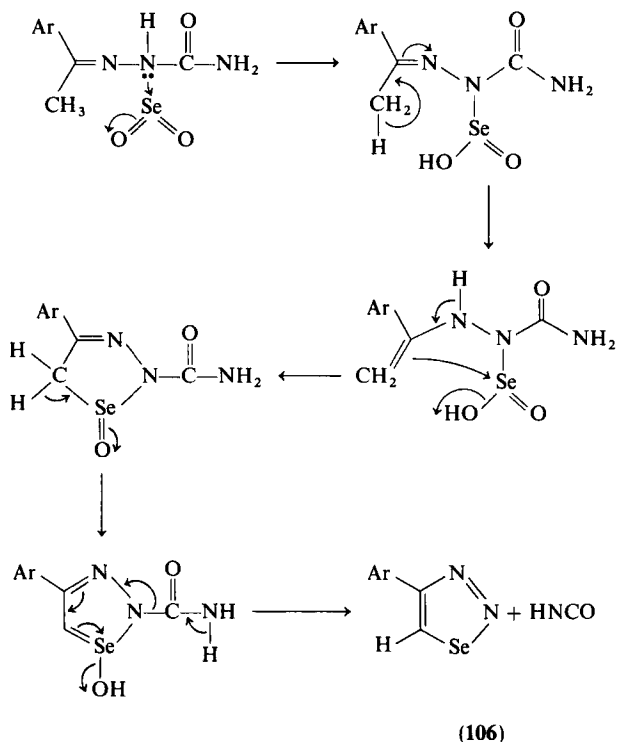
⁴⁹ D. L. Klayman and G. W. A. Milne, *Tetrahedron* **25**, 191 (1969).

⁵⁰ I. Lalezari, A. Shafiee, and M. Yalpani, *Tetrahedron Lett.*, 5105 (1969).

⁵¹ I. Lalezari, A. Shafiee, and M. Yalpani, *Angew. Chem., Int. Ed. Engl.* **9**, 464 (1970).

⁵² H. Meier and E. Voigt, *Tetrahedron* **28**, 187 (1972).

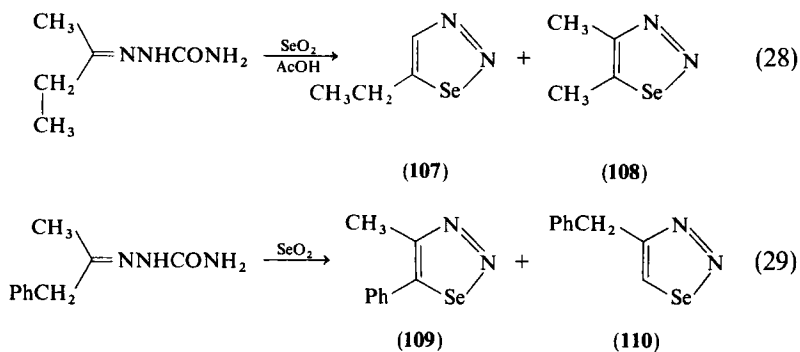
⁵³ I. Lalezari, A. Shafiee, and M. Yalpani, *J. Org. Chem.* **36**, 2836 (1971).



SCHEME 12

reacted to give the disubstituted selenadiazole **109** in higher yield than the 4-substituted derivative **110** [Eq. (29)].

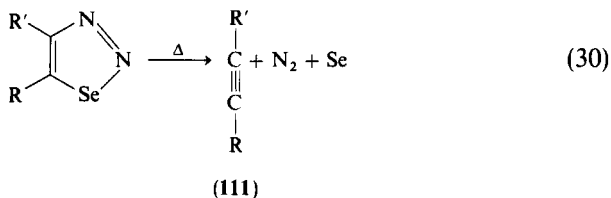
The NMR parameters of some aryl 1,2,3-selenadiazoles have been reported.⁵⁴ The chemical shifts of the 5-proton have been related to the aryl



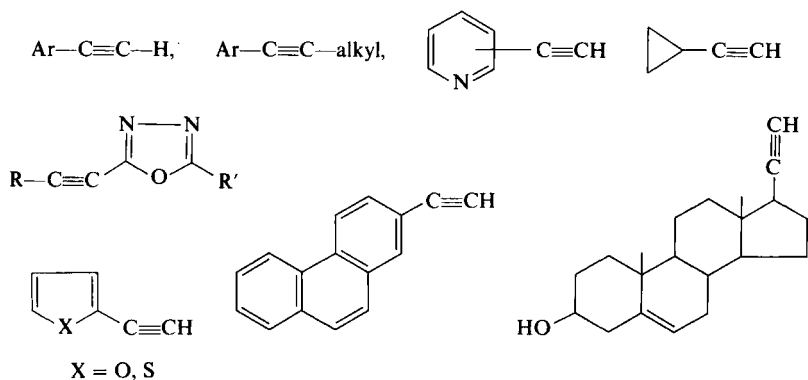
⁵⁴ A. Caplin, *J.C.S. Perkin I*, 30 (1974).

substituents. Heats of combustion and of sublimation of crystalline 4-phenyl-1,2,3-selenadiazole were determined by Arshadi and Shabrang.⁵⁵ Heats of formation and a C—Se bond energy of 57 kcal/mol were calculated.

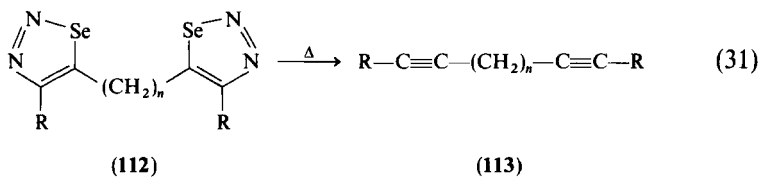
Unlike the 1,2,3-thiadiazole ring systems that are thermally stable, mono and disubstituted-1,2,3-selenadiazoles easily decompose on heating to give the acetylenes **111** in high yields⁵¹ (Eq. (30)).



The utility of this reaction is shown by the following types of acetylene



synthesized.^{51,56-58} Several diacetylenes (**113**) were also prepared by the thermal decomposition of the corresponding bis-selenadiazoles (**112**).⁵⁹ [Eq. 31].



⁵⁵ M. R. Arshadi and M. Shabrang, *J.C.S. Perkin II*, 1732 (1973).

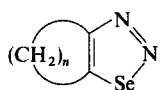
⁵⁶ I. Lalezari and A. Shafiee, unpublished results; see also A. I. Meyers, in "Heterocycles in Organic Synthesis," p. 85. Wiley, New York, 1974.

⁵⁷ M. Mirrashed, Pharm.D. Thesis, College of Pharmacy, Teheran University (1976); A. Shafiee, I. Lalezari, M. Mirrashed, and D. Nercesian, *J. Heterocycl. Chem.* **14**, 567 (1977).

⁵⁸ H. Golegolab and I. Lalezari, *J. Heterocycl. Chem.* **12**, 801 (1975).

⁵⁹ I. Lalezari, A. Shafiee, and H. Golegolab, *J. Heterocycl. Chem.* **10**, 655 (1973).

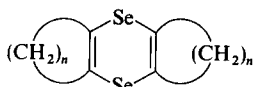
Starting with cycloalkanones, several cycloalkano-1,2,3-selenadiazoles (**114**) were prepared.^{52,60-62} When the cycloalkano ring contained eight or more carbons, they proved to be useful in the synthesis of cycloalkynes (**115**). When the ring size of the fused cycloalkane was eight or smaller, pyrolysis afforded the dicycloalka-1,4-diselenins (**116**).



(114)

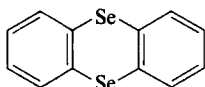


(115)

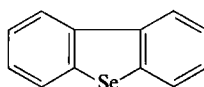


(116)

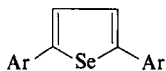
For $n = 4$, besides the corresponding 1,4-diselenins (**116**), the selenanthrene (**117**) and dibenzoselenophene (**118**) were also obtained when pyrolysis was carried out at 250°C for a prolonged period.⁶⁰



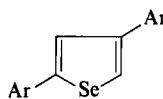
(117)



(118)

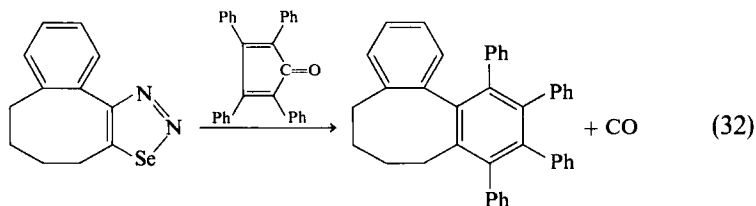


(119)



(120)

4-Aryl-1,2,3-selenadiazoles upon prolonged heating have also been converted into selenophenes **119** and **120**.^{63,64} Since these last compounds have also been obtained from the reaction of aryl acetylenes with Se, it is probable that the selenadiazole is not a direct precursor of the selenophenes.



(32)

⁶⁰ I. Lalezari, A. Shafiee, and M. Yalpani, *J. Heterocycl. Chem.* **9**, 1411 (1972).

⁶¹ H. Meier and J. Menzel, *J.C.S. Chem. Comm.*, 1059 (1971).

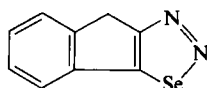
⁶² I. Lalezari and S. Sadeghi-Milani, *J. Heterocycl. Chem.*, **15**, 501 (1978).

⁶³ I. Lalezari, A. Shafiee, F. Rabet, and M. Yalpani, *J. Heterocycl. Chem.* **10**, 953 (1973).

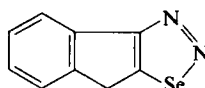
⁶⁴ I. Lalezari, A. Shafiee, and A. Rashidbeigi, *J. Heterocycl. Chem.* **12**, 57 (1976).

Meier and co-workers have shown that cycloalkano-1,2,3-selenadiazoles **114**, with $n = 6$ or smaller, on pyrolysis gave cycloalkynes which were trapped with tetraphenylcyclopentadienone, losing CO and forming fused tetraphenylbenzene derivatives [e.g., Eq. (32)].⁶⁵

Meier and co-workers⁶⁶ also allowed 1 and 2-indanone semicarbazones to react with selenium dioxide, to form the selenadiazole derivatives **121** and **122**, respectively.

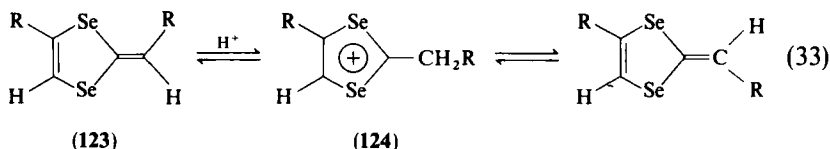


(121)

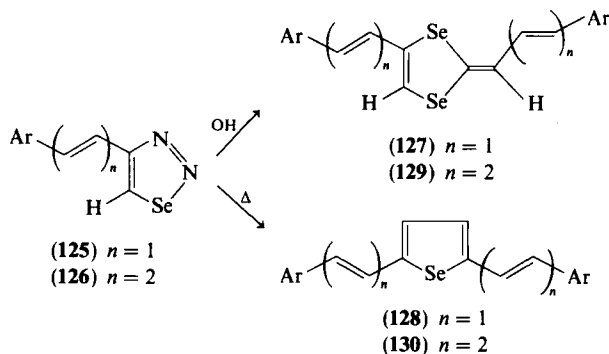


(122)

4-Substituted 1,2,3-selenadiazoles were found to react with a strong base to form 2, ω -disubstituted-1,4-diselenafulvenes **123**.⁶⁷ The stereochemistry of compounds **123** was established by NMR. It is suggested that the cis-trans isomerization of the 1,4-diselenafulvenes occurs via the diselenolium ion (**124**) [Eq. (33)].



1,4-Dialkenyl- or dialkadienyldiselenafulvenes of type **127** and **129** have been prepared through the base-catalyzed reaction of the correspondingly



SCHEME 13

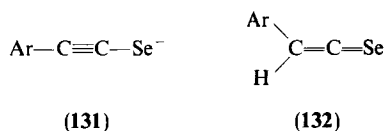
⁶⁵ H. Meier, M. Layer, and A. Zetzsche, *Chem. Ztg.* **98**, 460 (1975).

⁶⁶ H. Meier, S. Schniepp, and W. Combrink, *Chem. Ztg.* **99**, 461 (1975).

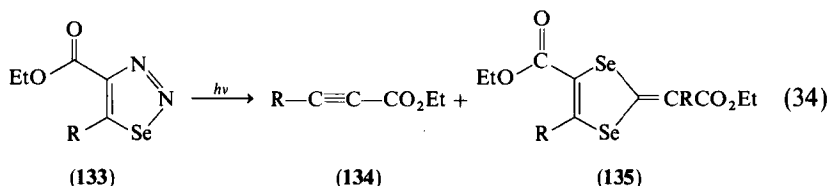
⁶⁷ I. Lalezari, A. Shafiee, and M. Yalpani, *J. Org. Chem.* **38**, 338 (1973).

substituted 1,2,3-selenadiazoles **125** and **126**.⁶⁸ Prolonged heating of the latter two compounds converted them into 2,5-disubstituted selenophenes **128** and **130** [(Scheme 13)].

The kinetics and detailed mechanism of the base-catalyzed decomposition of 4-aryl-1,2,3-selenadiazoles has been studied. It has been demonstrated that aryethynylselenolates (**131**) and selenoketenes (**132**) are intermediates in the diselenafulvene formation.⁶⁹



Light as well as heat decomposes the 1,2,3-selenadiazoles to give acetylenic compounds. Thus, photolysis of 4-carbethoxy-1,2,3-selenadiazoles (**133**) gave, in addition to the corresponding acetylenes (**134**) in high yield, small amounts of cis and trans mixtures of the 1,4-diselenafulvenes (**135**).⁷⁰ [Eq. 34].



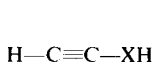
Laureni and co-workers⁷¹ have studied the photochemical decomposition of 1,2,3-selena and 1,2,3-thiadiazoles in argon or nitrogen matrix. In each case they could identify the products as the ethynylselenol or thiol (**136**) and the seleno- or thioketene (**137**). In addition, in the case of 1,2,3-selenadiazole acetylene was also detected. Using isotopically labelled substrates, they demonstrated that a major portion of the ethynylthiol formed from 1,2,3-thiadiazoles must have undergone an equilibration of the carbons, probably through the symmetrical thiirene intermediate (**138**). In the case of the selenium compound, however, their results showed that the selenirene is not on the route to the ethynylselenol (**136**, X = Se).

⁶⁸ I. Lalezari, A. Shafiee, and S. Sadeghi-Milani, *Proc. Int. Congr. Heterocycl. Chem.*, 6th, Teheran p. 414 (1977).

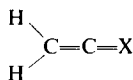
⁶⁹ M. H. Ghandehari, D. Davalian, M. H. Partovi, and M. Yalpani, *J. Org. Chem.* **39**, 3906 (1974).

⁷⁰ H. Meier and J. Menzel, *Tetrahedron Lett.*, 445 (1972).

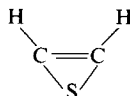
⁷¹ J. Laureni, A. Krantz, and R. A. Hajdu, *J. Am. Chem. Soc.* **98**, 7872 (1976).



(136)

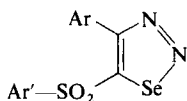


(137)

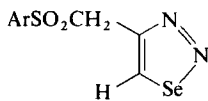


(138)

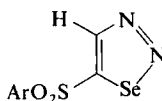
Photolysis of 4,5-diphenyl-1,2,3-selenadiazole in the presence of oxygen has been found to yield, besides diphenylacetylene in high yield, small amounts of tetraphenyl-1,4-diselenafulvene, benzil, and benzophenone.⁷² A series of 1,2,3-selenadiazoles substituted with arylsulfonyl moieties (139–141) have been prepared; they could not be converted into the corresponding acetylenes by pyrolysis. Arylsulfonylacetylenes **142** and **143** could, however, be prepared by the photolysis of 1,2,3-selenadiazoles.⁷³



(139)



(140)



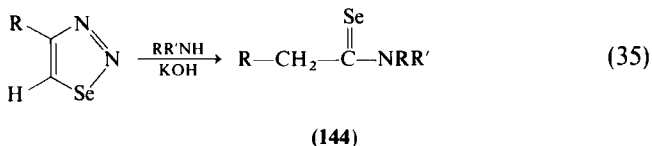
(141)



(142) R = Ph

(143) R = Me

The 1,2,3-selenadiazoles (139–141) have potent antibacterial and antifungal activity.⁷³ Similarly, 2-, 3-, and 4-pyridyl-1,4-diselenafulvenes as well as their parent 1,2,3-selenadiazoles are reported to have significant antibacterial activity.⁷⁴ The 1,2,3-selenadiazoles and ethynylselenolate salts derived from the selenadiazoles have been variously used as synthetic reagents. Thus, Malek-Yazdi and Yalpani⁷⁵ have prepared selenoamides (144) quantitatively from reaction of 4-substituted 1,2,3-selenadiazoles with amines containing potassium hydroxide [Eq. (35)].



The selenono esters **145** were also formed from the reaction of ethynylselenolates with alcohols.⁷⁶ Selenolesters, α -selenoketones, and selenoazoesters, of the type **146**, **147**, and **148**, have also been prepared by reacting

⁷² F. Malek-Yazdi and M. Yalpani, unpublished work (1976).

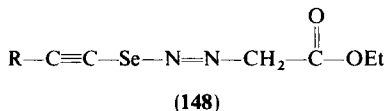
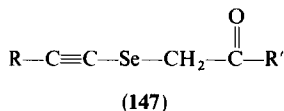
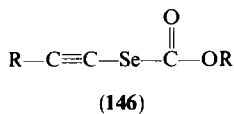
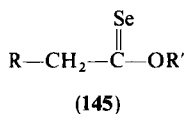
⁷³ I. Lalezari, A. Shafiee, J. Khorami, and A. Soltani, *J. Pharm. Sci.* **67**, 1336 (1978).

⁷⁴ I. Lalezari, A. Shafiee, and S. Yazdani, *J. Pharm. Sci.* **65**, 628 (1976).

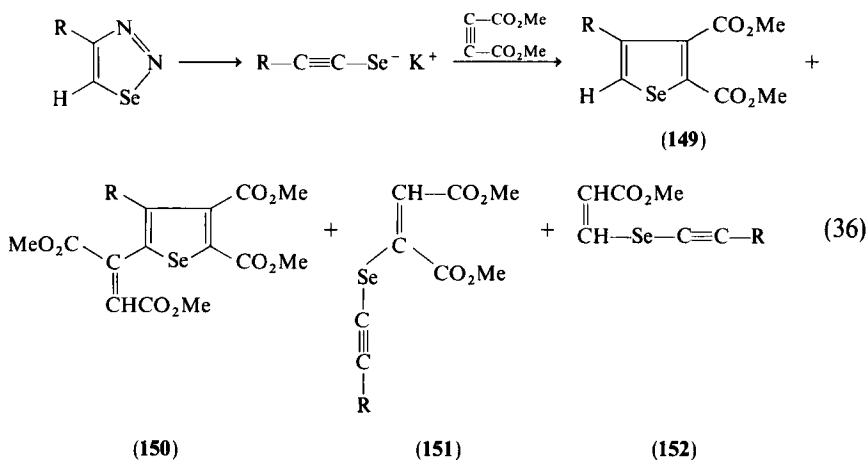
⁷⁵ F. Malek-Yazdi and M. Yalpani, *Synthesis*, 328 (1977).

⁷⁶ F. Malek-Yazdi and M. Yalpani, *J. Org. Chem.* **41**, 729 (1976).

potassium ethynylselenolates with chloroformic esters, α -haloketones, and diazoacetates, respectively.⁷⁷



Shafiee *et al.* have reported that 2-arylethynylselenolates react with dimethyl acetylenedicarboxylate to give, in addition to substituted selenophenes **149** and **150**, compounds **151** and **152**.⁷⁸ [Eq. 36].



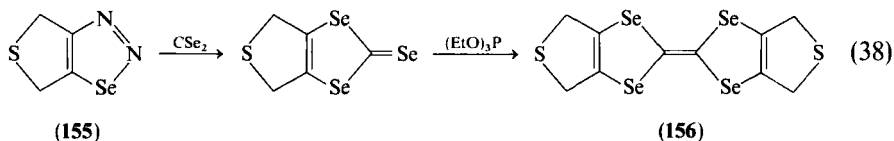
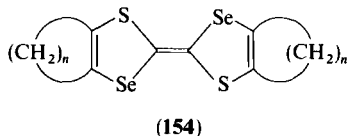
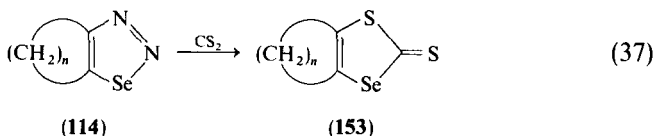
Cycloalkeno-1,2,3-selenadiazoles (**114**) have been converted into compounds **153** [Eq. (37)]. Subsequent reaction of the latter with triethylphosphine or triethyl phosphite gave *sym*-diselenadithiafulvalenes of type **154**.⁷⁹ Similarly, the synthesis of a tetraselenafulvene (**156**) has been reported through the reaction of the selenadiazole **155** with carbon diselenide and subsequent elimination of selenium with triethyl phosphite⁸⁰ [Eq. (38)].

⁷⁷ A. Shafiee, I. Lalezari, and F. Savabi, *Proc. Int. Congr. Heterocycl. Chem.* 6th, Teheran p. 176 (1977).

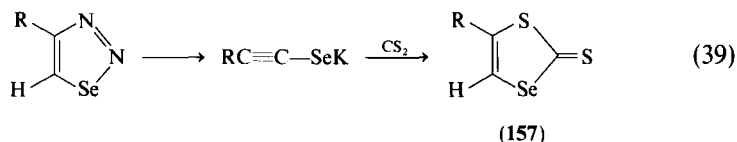
⁷⁸ A. Shafiee, I. Lalezari, and F. Savabi, *Synthesis*, 765 (1977).

⁷⁹ R. C. Wheland and J. L. Gillson, *J. Am. Chem. Soc.* **98**, 3916 (1976).

⁸⁰ C. Berg, K. Bechgaard, J. R. Andersen, and C. S. Jacobsen, *Tetrahedron Lett.*, 1719 (1976).



Shafiee, Lalezari, and Savabi have shown that 2-thioxo-1,3-thiaselenoles (**157**) could be synthesized from the corresponding 4-substituted-1,2,3-selenadiazoles via reaction of the selenolate with carbon disulfide at room



temperature.⁸¹ [Eq. (39)]. Charge transfer complexes of compounds **154** and **156** with tetracyanoquinodimethanes (TCNQ) have proved to be very interesting organic electrically conductive materials.^{79,80,82}

Muller and Odenigbo reported that the tetra-, penta-, hexa-, and octamethylene-1,2,3-selenadiazoles (**114**) react with rhodium complexes **158** and **159** to form substituted quinone derivatives **160** and **161**. The reaction of **158** (R = Ph) with trimethylene-1,2,3-selenadiazole (**114**; $n = 3$), however, gave the selenophene **162** and the 1,4-diselenin (**116**; $n = 3$)^{83,84} [Eq. (40)].

Iron carbonyl complex formation of 1,2,3-selenadiazoles has been studied by Rees and co-workers.^{85,86} Nitrogen extrusion by di-iron nonacarbonyl gave a mixture of two isomeric carbene iron complexes **163** and **164**. The

⁸¹ A. Shafiee, I. Lalezari, and F. Savabi, *Synthesis*, 674 (1977).

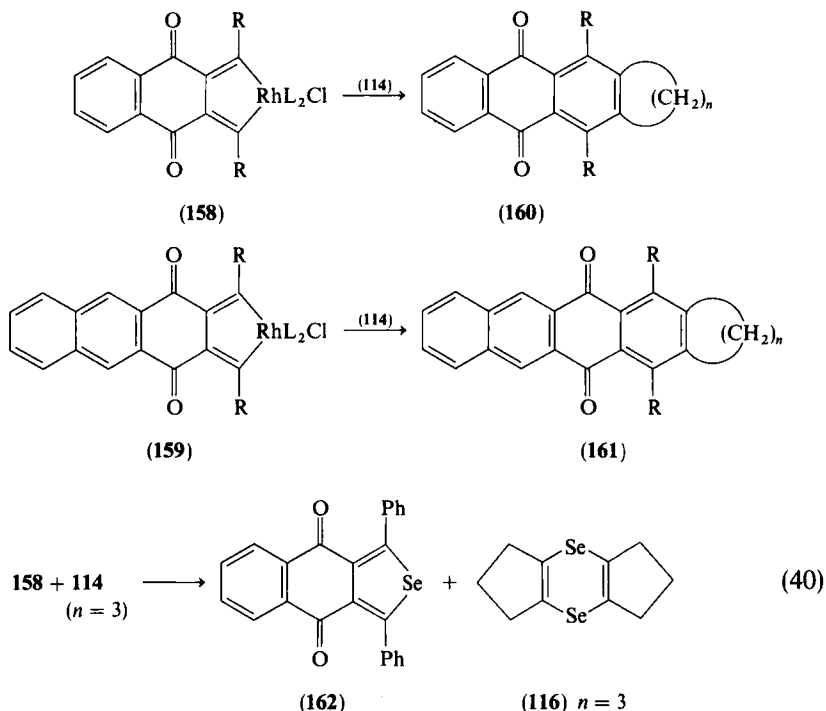
⁸² H. K. Spencer, M. W. Lakshmikanthan, M. P. Cava, and A. Garito, *J.C.S., Chem. Comm.*, 867 (1975).

⁸³ E. Müller and G. Odenigbo, *Justus Liebigs Ann. Chem.*, 1435 (1975).

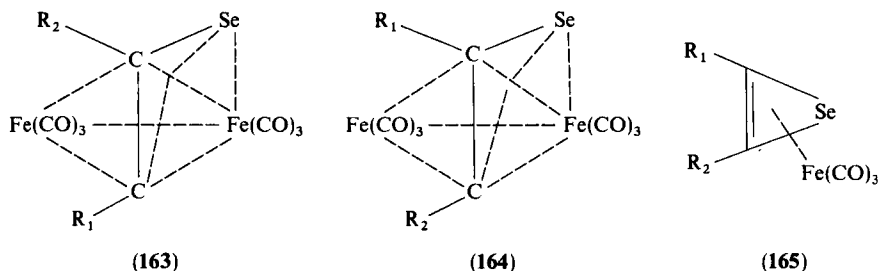
⁸⁴ E. Müller and G. Odenigbo, *Chem. Ztg.*, **97**, 662 (1973).

⁸⁵ P. G. Mente and C. W. Rees, *J.C.S., Chem. Comm.*, 418 (1972).

⁸⁶ T. L. Gilchrist, P. G. Mente, and C. W. Rees, *J.C.S. Perkin I*, 2165 (1972).



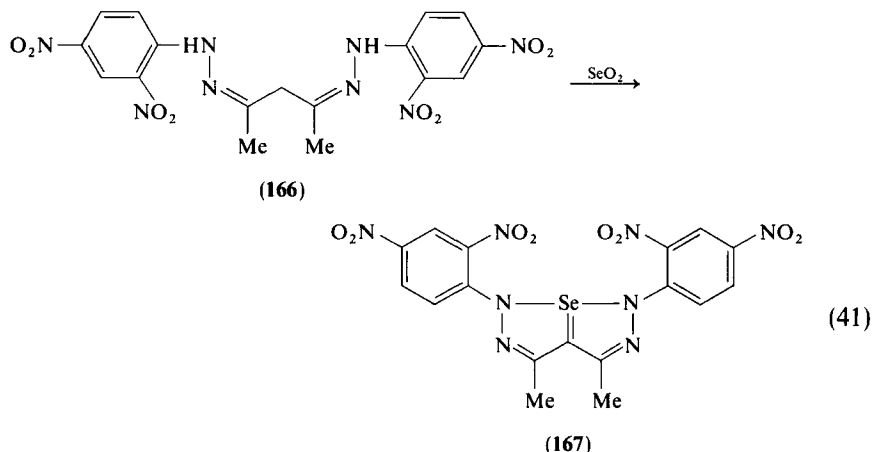
fact that a crossover product is formed is taken as evidence for the anti-aromatic symmetrical seleniren intermediate **165**. The structures of these complexes were established by X-ray analysis. Schrauzer and Kisch have studied the same reaction and arrived at similar conclusions.⁸⁷



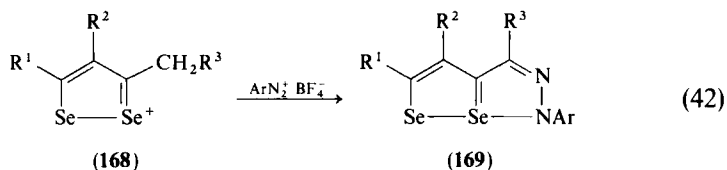
The synthesis of several novel hypervalent selenium heterocycles has been reported. Thus the 1,6-bis-(2,4-dinitrophenyl) 1,6-dihydro-3,4-dimethyl-1,2,3-selenadiazolo[5,1-*e*]selenadiazole-7-Se^{IV} (**167**) was obtained through

⁸⁷ G. N. Schrauzer and H. Kisch, *J. Am. Chem. Soc.* **95**, 2501 (1973).

selenium dioxide oxidation of 2,4-pentanedione bis-2,4-dinitrophenylhydrazone (**166**).⁸⁸ [Eq. (41)].



Several 1-aryl-6,6a-diselena-1,2-diazapentalenes (**169**) were made by allowing 3-methyl(ene)-1,2-diselenolium salts (**168**) to react with arene-diazonium fluoroborates [Eq. (42)]. The structure of the sulfur analog was established by X-ray analysis.⁸⁹



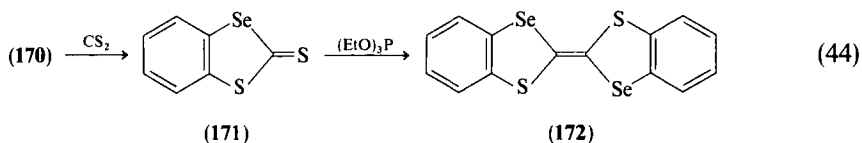
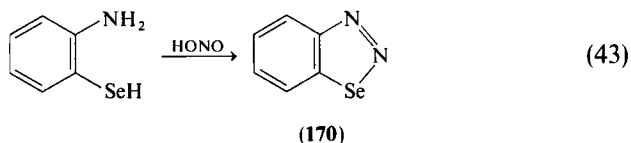
2. 1,2,3-Benzoselenadiazoles

The synthesis of 1,2,3-benzoselenadiazole (**170**) and its 4- and 5-methyl derivatives reported by Keimatsu and Satoda in 1935 constituted the first members of this ring system.⁹⁰ [Eq. (43)]. No further work on this compound was reported until 1975, when the unsubstituted compound was used to make the two isomers of the dibenzodiselenadithiafulvalene (**172**) by the reaction of **170** with carbon disulfide and subsequent reaction of intermediate **171** with triethyl phosphite⁸² [Eq. (44)].

⁸⁸ M. Perrier and J. Vialle, *Bull. Soc. Chim. Fr.*, 4591 (1971).

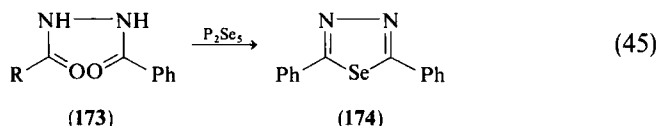
⁸⁹ R. M. Christie and D. H. Reid, *J.C.S. Perkin I*, 228 (1976).

⁹⁰ S. Keimatsu and I. Satoda, *Yakugaku Zasshi* **55**, 233 (1935) [*CA* **31**, 6661 (1937)].

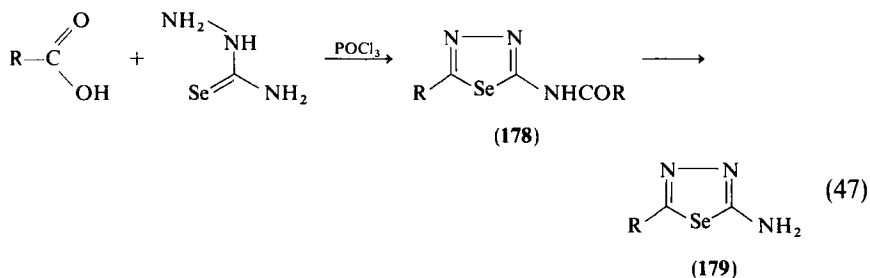
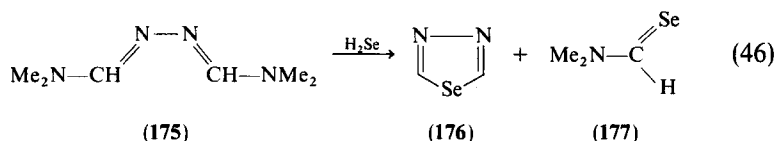


3. 1,3,4-Selenadiazoles

2,5-Disubstituted-1,3,4-selenadiazoles (**174**) were obtained by Stolle and Gutmann in 1904, through the reaction of *N,N'*-diacylhydrazines (**173**) with phosphorus pentaselenide.⁹¹ [Eq. (45)].



Unsubstituted 1,3,4-selenadiazole (**176**) was synthesized by Kendall and Olofson by the reaction of *N,N*-dimethylformamide azine (**175**) with hydrogen selenide in the presence of small amounts of pyridine.⁹² In addition to **176**, *N,N*-dimethylselenoformamide (**177**) was formed in equal yield. [Eq. (46)].

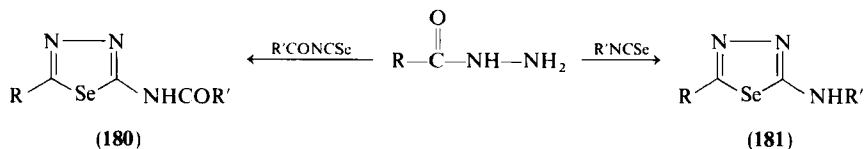


⁹¹ R. Stolle and L. Gutmann, *J. Prakt. Chem.* **69**, 509 (1904).

⁹² R. V. Kendall and R. A. Olofson, *J. Org. Chem.* **35**, 806 (1970).

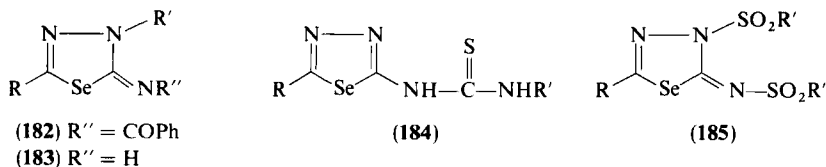
2-Amino-1,3,4-selenadiazoles (**179**) were prepared by Lalezari and Shafiee from selenosemicarbazide, a carboxylic acid and phosphorus oxychloride. The initially formed 2-acylamino derivatives (**178**) were hydrolyzed to their corresponding 2-amino compounds⁹³ [Eq. (47)].

1,3,4-Selenadiazoles with 2-amino substitution (**180** and **181**) were also prepared by Bulka and co-workers by the reaction of acylhydrazides with acyl or alkyl isoselenocyanates^{94,95} (Scheme 14).

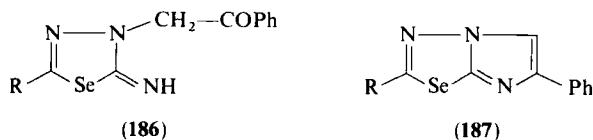


SCHEME 14

Several reactions of 2-amino- and 2-acylamino-1,3,4-selenadiazoles have been reported. Thus, alkylation of the potassium salt of **180** with methyl and ethyl iodide gave the acylimine **182**. The latter upon hydrolysis formed **183**.⁹⁴ Reaction of **179** with alkyl or aryl isothiocyanates resulted in the formation of thioureas (**184**), while sulfonyl chlorides gave the disulfonyl derivatives **185**. Diazotization and coupling reactions of **179** are also reported.⁹²



Alkylation of **179** with α -haloketones gave the 3-alkylated imine derivative **186**. The latter was cyclized to 2-substituted-6-phenylimidazo[2,1-*b*]-1,3,4-selenadiazoles (**187**).⁹³



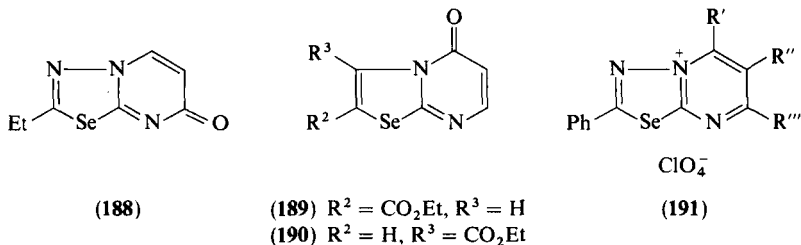
Different types of fused ring system resulted from the reaction of 5-ethyl derivative of **179** with ethyl propiolate. Besides the 2-ethyl-7*H*-1,3,4-

⁹³ I. Lalezari and A. Shafiee, *J. Heterocycl. Chem.* **8**, 835 (1971).

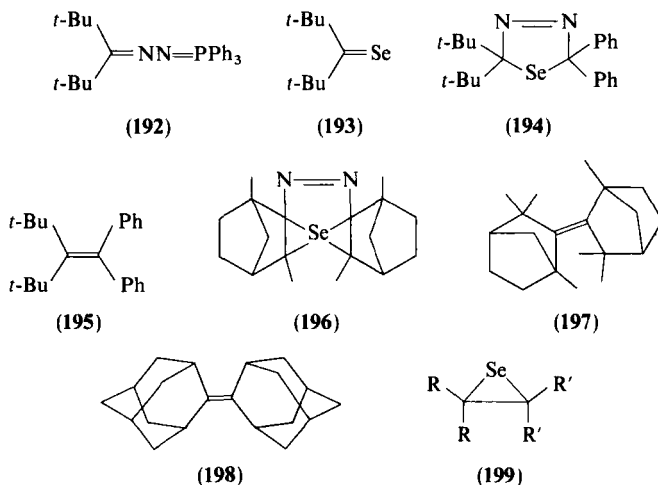
⁹⁴ E. Bulka, D. Ehlers, and H. Storm, *J. Prakt. Chem.* **315**, 164 (1973).

⁹⁵ E. Bulka and D. Ehlers, *J. Prakt. Chem.* **315**, 510 (1973).

selenadiazolo[3,2-*a*]pyrimidin-7-one (**188**), 2- or 3-carbethoxy-5*H*-selenazolo[3,2-*a*]pyrimidin-5-one (**189** or **190**) was also formed, along with propionitrile.⁹⁶ The selenadiazolopyrimidium perchlorates **191** were prepared by the reaction of the 5-phenyl derivative of **179** with 1,3-dicarbonyl compounds.⁹⁷



Back and co-workers⁹⁸ have prepared the 2,2,5,5-tetrasubstituted Δ^3 -1,3,4-selenadiazoline **194** and used it in an elegant method for the preparation of sterically very crowded olefins. For this purpose di-*t*-butylketone triphenylphosphoranylidenehydrazone (**192**) was heated with selenium powder to give the selenoketone **193**. Reaction of the latter with diphenyldiazomethane gave the 1,3,4-selenadiazoline **194**. This compound on heating gave the olefin **195**. In a similar way were obtained **196** and **197** and biadamantylidene (**198**). The thermal decomposition of the 1,3,4-selenadiazolines is thought to proceed through the corresponding episelenide (**199**).



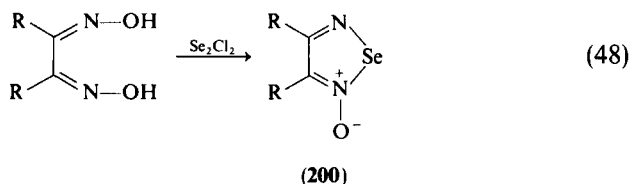
⁹⁶ A. Shafiee and I. Lalezari, *J. Heterocycl. Chem.* **12**, 675 (1975).

⁹⁷ V. A. Chuiguk, D. I. Sheiko, and V. G. Glushkov, *Khim. Geterotsykl. Soedin.*, 1435 (1974) [*CA* **82**, 43317 (1975)].

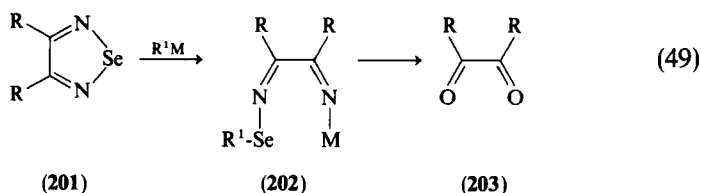
⁹⁸ T. G. Back, D. H. R. Barton, M. R. Britten-Kelly, and F. S. Guziec, *J.C.S. Perkin I*, 2079 (1976).

4. 1,2,5-Selenadiazoles

Since the last review of this system only one 1,2,5-selenadiazole without a fused ring has been reported. When a 1,2-diketone dioxime is treated with selenium monochloride in dimethylformamide, the 1,2,5-selenadiazole *N*-oxide (**200**) is formed⁹⁹ [Eq. (48)].



While unsubstituted or monosubstituted 1,2,5-selenadiazoles are reportedly quite stable to aqueous or alcoholic hydroxide solutions, the disubstituted derivatives (**201**) react quite readily even at -70° with Grignard reagents or alkyllithiums. The reaction is believed to proceed through a selenoether intermediate (**202**) to give 1,2-dicarbonyl compounds (**203**)¹⁰⁰ [Eq. (49)].



The most convenient method for the synthesis of fused 1,2,5-selenadiazoles is still considered to be the reaction of 1,2-diamino aromatic substrates with selenium dioxide, reported in 1889 by Hinsberg.¹⁰¹ Using this method selenolo[3,2-*e*]-2,1,3-benzoselenadiazole (**204**), naphtho[1,2-*c*][1,2,5]selenadiazole (**205**), and naphtho[2,3-*c*][1,2,5]selenadiazole (**206**) were prepared through the corresponding 1,2-diamino compounds.¹⁰² In recent years, however, selenoxychloride has been used for weakly basic amines, where the Hinsberg method had given poor results. Using this new reagent Komin and Carmack synthesized the [1,2,5]selenadiazolo[3,4-*c*][1,2,5]thiadiazole (**207**) and the [1,2,5]selenadiazolo[3,4-*b*]quinoxaline (**208**) from the appropriate 1,2-diamino compounds.¹⁰³

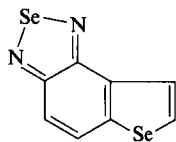
⁹⁹ C. L. Pedersen, *J.C.S., Chem. Comm.*, 704 (1974).

¹⁰⁰ V. Bertini, A. De Munno, A. Menconi, and A. Fissi, *J. Org. Chem.* **39**, 2294 (1974).

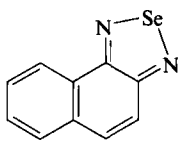
¹⁰¹ O. Hinsberg, *Chem. Ber.* **22**, 862, 2895 (1889).

¹⁰² P. Jacquignon, G. Marechal, M. Renson, A. Ruwet, and D. Hien, *Bull. Soc. Chim. Fr.*, 677 (1973).

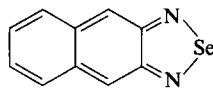
¹⁰³ A. P. Komin and M. Carmack, *J. Heterocycl. Chem.* **13**, 13 (1976).



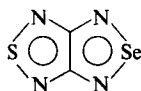
(204)



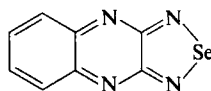
(205)



(206)

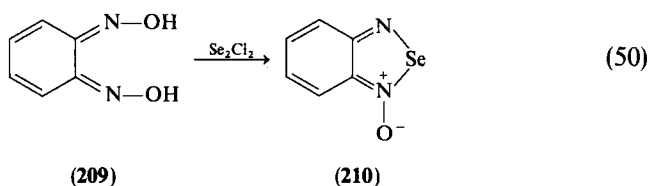


(207)

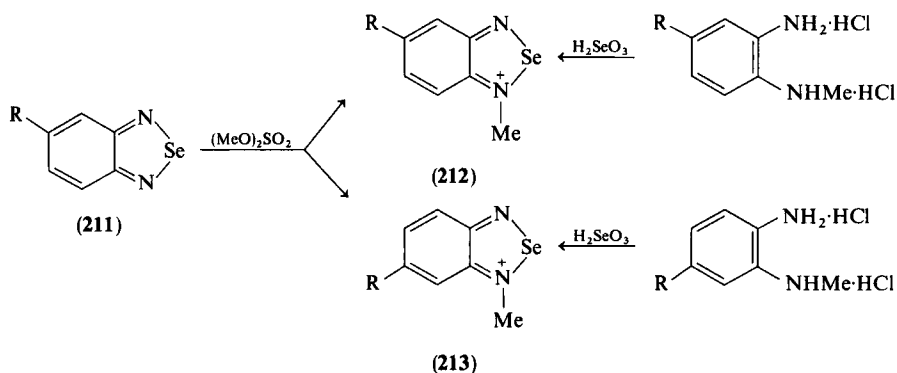


(208)

2,1,3-Benzoselenadiazole-*N*-oxide (**210**) was prepared by Pedersen⁹⁹ through the reaction of *o*-benzoquinone dioxime (**209**) with selenium monochloride [Eq. (50)].



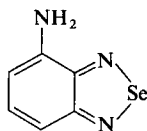
Alkylation of 5-substituted-2,1,3-benzoselenadiazoles (**211**) with dimethyl sulfate afforded two isomeric 2,1,3-benzoselenadiazolium salts **212** and **213**. Their structures were confirmed through independent synthesis¹⁰⁴ (Scheme 15).



SCHEME 15

¹⁰⁴ G. I. Eremeeva, B. K. Strelets, and L. S. Efros, *Khim. Geterotsikl. Soedin.*, 276 (1975) [*CA* **82**, 156192 (1975)]; *Khim. Geterotsikl. Soedin.*, 340 (1976) [*CA* **85**, 21234 (1976)].

Catalytic amination of 2,1,3-benzoselenadiazole with hydroxylamine and sulfuric acid in the presence of vanadium pentoxide afforded 4-amino-2,1,3-benzoselenadiazole (**214**).¹⁰⁵

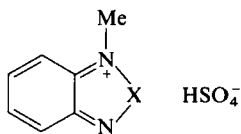


(214)

The photolysis of 2,1,3-benzoselenadiazole has resulted in the formation of a mixture of the three geometric isomers of mucononitrile.¹⁰⁶

The reaction of *o*-phenylenediamine derivatives with quadrivalent selenium, which affords 2,1,3-benzoselenadiazoles, has been used as a very sensitive analytical method for the detection of selenium in water, food, and animal tissue.^{107,108} The 2,1,3-benzoselenadiazoles have also been used in coulometric titration of palladium. The stoichiometry of the reaction of the diazole with Pd^{2+} is reported to be 2:1.¹⁰⁹

Several NMR studies of the substituted 2,1,3-selenadiazoles have been reported. Thus Katritzky and Takeuchi¹¹⁰ have studied the effect of substituents on the coupling constants of the aromatic ring protons. The *N*-methyl chemical shift in quaternized 2,1,3-benzoselenadiazole (**215**) and its congeners have been studied. The shifts appear to be determined by resonance from the heteroatom, the order of donating ability being $\text{NMe} > \text{O} > \text{S} \sim \text{Se}$.¹¹¹



(215)

X = NMe, O, S, Se

¹⁰⁵ V. A. Sergeev, V. G. Pesin, and N. M. Kotikova, *Khim. Geterotsikl. Soedin.*, 328 (1972) [*CA* 77, 61898 (1972)].

¹⁰⁶ M. Arvanaghi and M. Yalpani, unpublished work. (1976).

¹⁰⁷ K. Nakamo, Y. Sayoto, M. Tonomura, and Y. Ose, *Eisei Kagaku* 18, 237 (1972) [*CA* 78, 67735 (1973)].

¹⁰⁸ Y. Shimoishi, *Bull. Chem. Soc. Jpn.* 47, 997 (1974).

¹⁰⁹ V. S. Tsveniashvili, N. S. Khartasi, V. N. Gaprindashvili, and T. B. Bezhushevili, *Soobshch. Akad. Nauk. Gruz. SSR* 65, 317 (1972) [*CA* 77, 42714 (1972)].

¹¹⁰ A. R. Katritzky and Y. Takeuchi, *J.C.S. Perkin II*, 1682 (1972).

¹¹¹ M. Davis, L. W. Deady, and E. Homfeld, *J. Heterocycl. Chem.* 11, 1011 (1974).

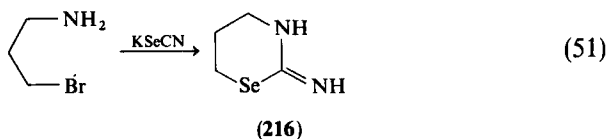
Cheeseman and Turner¹¹² studied ¹³C chemical shifts and C—H coupling constants for 2,1,3-benzoselenadiazoles. The isotopic esr spectra of a number of selenium-containing aromatic radicals including 2,1,3-benzoselenadiazoles have been reported.¹¹³ The mass spectral fragmentation of 2,1,3-benzoselenadiazoles has been described by Pedersen and Moeller.¹¹⁴ The redox behavior of this heterocycle is discussed by Shermann and co-workers.¹¹⁵ The importance of the various mesomeric forms of the 2,1,3-benzoselenadiazoles and their oxygen and sulfur congeners has been investigated by electrical dipole moment measurements of substituted derivatives. The mesomeric charge transfer is reported to increase from the oxygen to the selenium compound, being nearly undetected in 2,1,3-benzoxadiazole derivatives and very pronounced in the selenium compound.¹¹⁶ Heats of combustion data of 2,1,3-benzoselenadiazole have been obtained by Arshadi and compared with the sulfur and oxygen heterocycles.¹¹⁷ The effect of the pyridine and pyrimidine ring on the polarographic reduction of 2,1,3-selenadiazoles have been studied.¹¹⁸

III. Six-Membered Selenium–Nitrogen Heterocycles

A. SIX-MEMBERED SELENIUM HETEROCYCLES WITH ONE NITROGEN ATOM

1. 1,3-Selenazines

The first derivative of this ring system, 2-imino-2,3,5,6-tetrahydro-1,3-selenazine (**216**), was obtained through the reaction of 1-bromo-3-amino-propane with potassium selenocyanate.¹¹⁹ [Eq. (51)].



¹¹² G. W. H. Cheeseman and C. J. Turner, *Org. Magn. Reson.* **6**, 430 (1974).

¹¹³ M. F. Chiu and B. C. Gilbert, *J.C.S. Perkin II*, 258 (1973).

¹¹⁴ C. L. Pedersen and J. Moeller, *Acta Chem. Scand., Ser. B29*, 483 (1975).

¹¹⁵ E. O. Shermann, S. M. Lambert, and K. Pilgram, *J. Heterocycl. Chem.* **11**, 763 (1974).

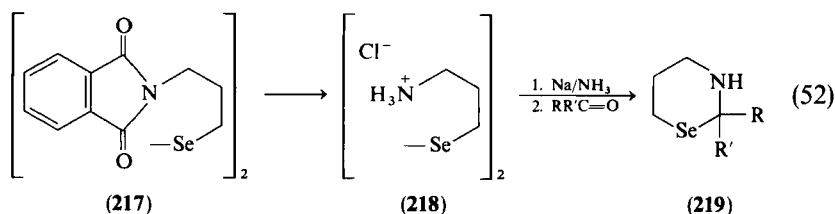
¹¹⁶ F. L. Tobiason, L. Huestis, C. Chandler, S. E. Pedersen, and P. Peters, *J. Heterocycl. Chem.* **10**, 773 (1973).

¹¹⁷ M. R. Arshadi, unpublished work (1975).

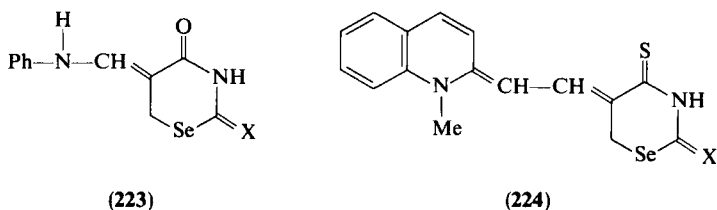
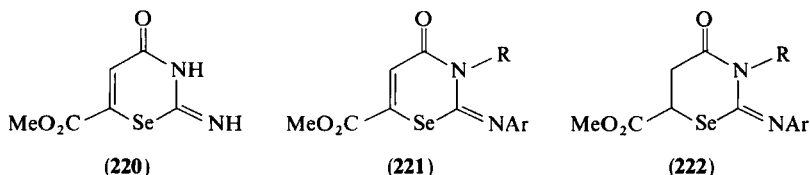
¹¹⁸ V. Sh. Tsvenishvili, L. A. Tskalobadze, and V. N. Gaprindashvili, *Soobshch. Akad. Nauk Gruz. SSR*, **71**, 625 (1973) [*CA* **80**, 70049 (1974)].

¹¹⁹ W. Beringer, *Chem. Ber.* **23**, 1003 (1890).

More recently, perhydro-1,3-selenazines (**219**) were prepared by the reaction of bis-(3-phthalimidopropyl)diselenide (**217**) with hydrazine hydrochloride to give the diselenide **218**. Reduction of the latter with sodium in liquid ammonia followed by treatment with aldehydes or ketones gave the selenazines **219**¹²⁰ [Eq. (52)].



Selenourea and 1-aryl and 1,3-diarylselenoureas reacted with acetylenedicarboxylic acid and its dimethyl ester to give 3,4-dihydro-2-imino-2*H*-1,3-selenazin-4-one-6-carboxylic acid derivatives, e.g., **220** and **221**. The structure of **221** was deduced from that of its hydrogenation product **222**.¹²¹



Reaction of the 1,3-selenazine derivative **223** with *N*-methylquinaldinium salts is reported to give the quinolinidene derivative **224** (X = S) and its oxo derivative (X = O). Lepidinium derivatives behaved similarly.¹²²

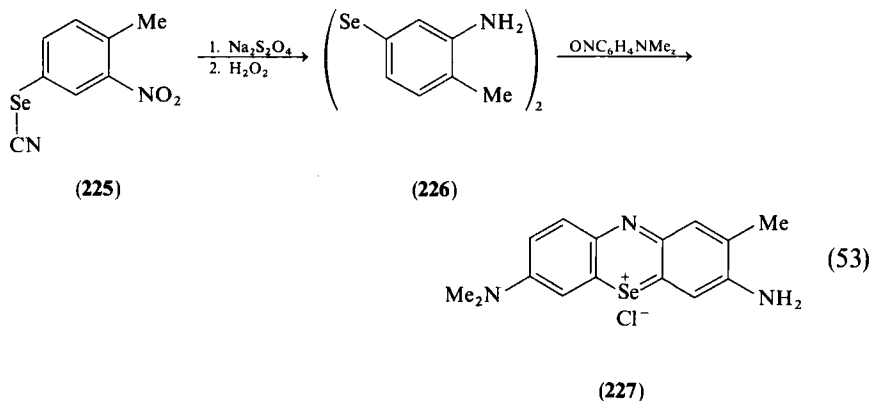
¹²⁰ C. Draguet and M. Renson, *C. R. Acad. Sci., Ser. C* **274**, 1637 (1972).

¹²¹ A. Shafiee, F. Assadi, and I. V. Cohen, *J. Heterocycl. Chem.*, **15**, 39 (1978).

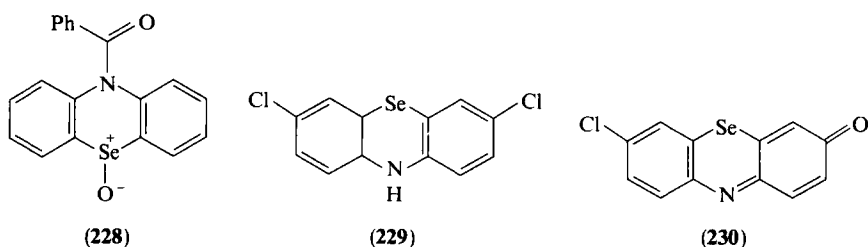
¹²² V. E. Kononenko, B. E. Zhitar, and S. N. Baranov, *Khim. Geterotsikl. Soedin.*, 1493 (1973) [*CA* **80**, 82817 (1974)].

2. 1,4-Selenazines

3-Amino-7-dimethylamino-2-methylphenoselenazin-5-ium (selenotoluidine blue) (**227**) was prepared through the following steps. Reduction of 4-methyl-3-nitrophenylselenocyanate (**225**) with sodium dithionite followed by oxidation with H_2O_2 gave bis-(4-methyl-3-aminophenyl)diselenide (**226**). Cyclization of the latter with *N,N*-dimethylamino-*p*-nitrosoaniline hydrochloride gave **227**¹²³ [Eq. (53)].



10-Benzoyl-10*H*-phenoselenazine 5-oxide (**228**) was prepared from 10-benzoyl-10*H*-phenoselenazine and phenyl iodosoacetate. The 10-(2-furoyl) 5-oxide was prepared similarly.¹²⁴



Oxidation of 3,7-dichloro-10*H*-phenoselenazine (**229**) with iodine in DMSO gave 7-chloro-3*H*-phenoselenazin-3-one (**230**).¹²⁵

¹²³ J. T. Groves, S. M. Lindenauer, B. J. Haywood, J. A. Knal, and J. S. Schultz, *J. Med. Chem.* **17**, 902 (1974).

¹²⁴ B. D. Podolesov and V. B. Jordanovska, *Croat. Chem. Acta* **44**, 411 (1972) [*CA* **78**, 43431 (1973)].

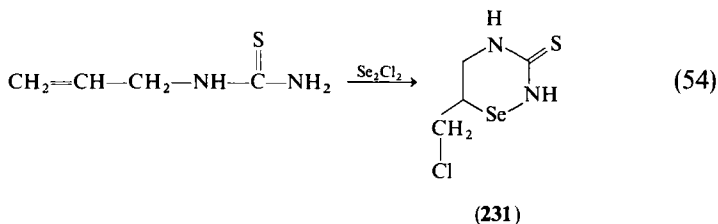
¹²⁵ J. Sugita and Y. Tsujino, Japanese Patent 73 22,714 [*CA* **80**, 3543 (1974)].

Some of the properties of phenoselenazines, including polarography, electric resistivity, ESR, NMR, crystal structure, and molecular conformation, nuclear spin coupling constants, the cation radical equilibrium constant and the heat of dimerization, the ESR spectrum and mechanism of photo-reduction, and the semiconduction behavior of phenoselenazine-iodine complexes, have been reported.¹²⁶⁻¹³⁴

B. SIX-MEMBERED SELENIUM HETEROCYCLES WITH TWO NITROGEN ATOMS

1. 1,2,4-Selenadiazines

The synthesis of only two selenadiazine derivatives have been described. The 6-chloromethyldihydro(2*H*)-1,2,4-selenadiazine-3(4*H*)-thione (**231**) was prepared by Apostolescu through treatment of allylthiourea with selenium monochloride.¹³⁵ [Eq. (54)]. The NMR spectrum of **231** and the activation energy for the decomposition and dehydration of its dihydrate have been studied.¹³⁶



¹²⁶ J. Komenda, *Scr. Fac. Sci. Nat. Univ. Purkyninae Brun.* **1**, 1 (1971) [*CA* **76**, 98804 (1972)].

¹²⁷ Y. Matsunaga and Y. Suzuki, *Bull. Chem. Soc. Jpn.* **45**, 3375 (1972).

¹²⁸ M. F. Chiu, B. C. Gilbert, and P. Hanson, *J.C.S. (B)*, 1700 (1970).

¹²⁹ L. Kamenov and D. Simov, *God. Sofii. Univ., Khim. Fak.* **64**, 111 (1969-1970) [*CA* **78**, 147194 (1973)].

¹³⁰ F. Bernier, A. Conde, and R. Marquez, *Acta Crystallogr., Sect. B* **30**, 1332 (1974).

¹³¹ V. Galasso and A. Bigotto, *Org. Magn. Reson.* **6**, 475 (1974).

¹³² Y. Matsunaga and T. Tanaka, *Bull. Chem. Soc. Jpn.* **48**, 1043 (1975).

¹³³ E. Vogelmann, H. Schmidt, U. Steiner, and H. E. A. Kramer, *Z. Phys. Chem. (Frankfurt am Main)* **94**, 101 (1975) [*CA* **83**, 12149 (1975)].

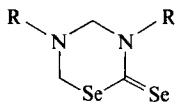
¹³⁴ Y. Matsunaga, *Energy Charge Transfer Org. Semicond., Proc. U.S.-Jpn. Semin.* p. 189 (1973) [*CA* **83**, 177966 (1975)].

¹³⁵ M. Apostolescu, *Bul. Inst. Politeh. Iasi* **20**, 9 (1974) [*CA* **82**, 112049 (1975)].

¹³⁶ M. Apostolescu, *Bul. Inst. Politeh. Iasi, Sect. 2* **20**, 7 (1974) [*CA* **83**, 205564 (1975)].

2. 1,3,5-Selenadiazines

The reaction of primary amines with carbon diselenide and formaldehyde has resulted in the formation of tetrahydro-1,3,5-selenadiazine-2-selenones (**232**).¹³⁷

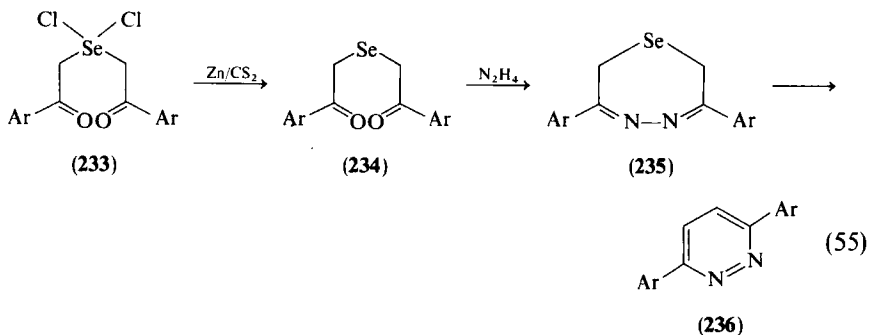


(232)

R = PhCH₂ or *p*-EtOC₆H₄

IV. Miscellaneous Selenium–Nitrogen Heterocycles

2,7-Dihydro-1,4,5-selenadiazepines (**235**) were obtained by Ajello through the interaction of hydrazine with β,β' -selenadiacetophenones (**234**). The latter was obtained by reduction of the corresponding bis(dichloroselenoacetophenones) (**233**). The selenadiazepines (**235**) underwent facile ring contraction when heated in ethylene glycol, to give the corresponding pyridazines (**236**).¹³⁸ [Eq. (55)].

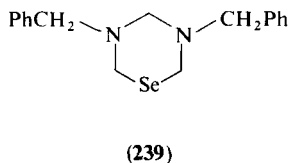
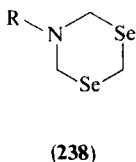
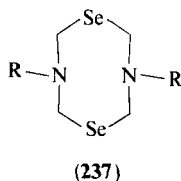


The perhydropyridoselenadiazocines **237**, the perhydropyridoselenazines **238**, and the perhydropyridoselenadiazine **239**, were prepared by the reaction of primary amines with formaldehyde and hydrogen selenide.¹³⁹

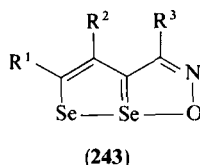
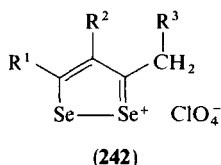
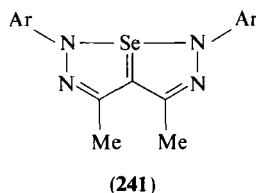
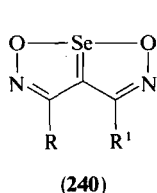
¹³⁷ G. Suchar and P. Kristian, *Chem. Zvesti* **28**, 425 (1974) [*CA* **81**, 120586 (1974)].

¹³⁸ E. Ajello, *J. Heterocycl. Chem.* **9**, 1427 (1972).

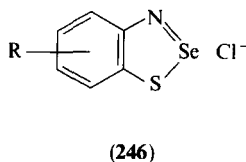
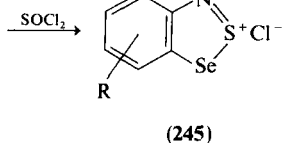
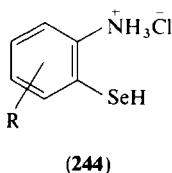
¹³⁹ C. Draguet, H. D. Fiorentina, and M. Renson, *C. R. Acad. Sci., Ser. C* **274**, 1700 (1972).



Derivatives of the 2,5-diaza-1,6-dioxa-6a-selena(Se^{IV})pentalene (**240**) and 1,2,5,6-tetraaza-6a-selena(Se^{IV})pentalene (**241**) systems were obtained through the oxidation of β -diketone dioximes and diphenylhydrazones, respectively, with selenium dioxide.¹⁴⁰ Another selena(Se^{IV})pentalene type (**243**) has been synthesized by treatment of the diselenolium salts **242** with sodium nitrite in acetic acid-acetonitrile.¹⁴¹



2,1,3-Benzothiaselenazolium chlorides (**245**) were prepared in good yield by the reaction of thionyl chloride with the corresponding *o*-aminoselenophenol hydrochlorides (**244**).¹⁴² The isomeric 1,2,3-benzothiaselenazolium salts (**246**) were obtained by treatment of the corresponding benzodithiazolium chlorides with H_3SeO_3 in acetic acid-ethanol.¹⁴³



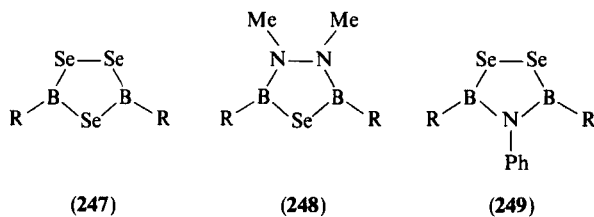
¹⁴⁰ M. Perrier and J. Vialle, *Bull. Soc. Chim. Fr.*, 4591 (1971).

¹⁴¹ J. G. Dingwall, A. R. Dunn, D. H. Reid, and K. O. Wade, *J.C.S. Perkin I*, 1360 (1972).

¹⁴² Yu. I. Akulin, B. Kh. Strelets, and L. S. Efros, *Khim. Geterotsikl. Soedin.*, 275 (1975) [*CA* **82**, 156191 (1975)].

¹⁴³ L. S. Efros, B. Kh. Strelets, and Yu. I. Akulin, *Khim. Geterotsikl. Soedin.*, 1361 (1976) [*CA* **86**, 72527 (1977)].

Two boron–nitrogen–selenium heterocycles of types **248** and **249** were obtained when the triselenodiboronolanes (**247**) were treated with 1,2-dimethylhydrazine and aniline, respectively. The triselenadiborolanes required were obtained from the reaction of RBI_2 and selenium.¹⁴⁴



¹⁴⁴ W. Siebert and F. Riegel, *Chem. Ber.* **106**, 1012 (1973).

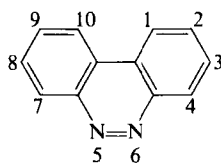
Benzo[*c*]cinnolines

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I. Introduction; Scope of the Review



(1)

The parent compound (1) was discovered in 1891 by Täuber, who called it diphenyleneazone,¹ and later phenazone.² Unfortunately, the latter name was at one time also used for 2,3-dimethyl-1-phenylpyrazol-5-one (anti-pyrine). More recently 1 has been called 3,4-benzocinnoline and now benzo-[c]cinnoline, using *Chemical Abstracts* nomenclature. The numbering shown is that currently used; Beilstein's Handbuch employed numbering analogous to that used for phenanthrene.

The present review concentrates mainly on work carried out during the past 25 years, as two brief reviews, covering the literature up to 1955, have appeared previously.^{3,4}

II. Reactions Leading to the Benzo[c]cinnoline Ring System

A. THE CYCLIZATION OF BIPHENYL DERIVATIVES

1. 2-Substituted Biphenyls

When certain derivatives of 2-aminobiphenyl, having activating substituents in the other ring, are diazotized, they undergo internal coupling to give benzo[c]cinnolines. For example, aqueous solutions of the diazonium chloride (2) from 2-amino-3'-methoxybiphenyl deposit 2-methoxybenzo[c]cinnoline on keeping or on buffering with sodium acetate [Eq. (1)].^{5,6} While it is possible to convert this diazonium salt into the corresponding iodo

¹ E. Täuber, *Chem. Ber.* **24**, 3081 (1891).

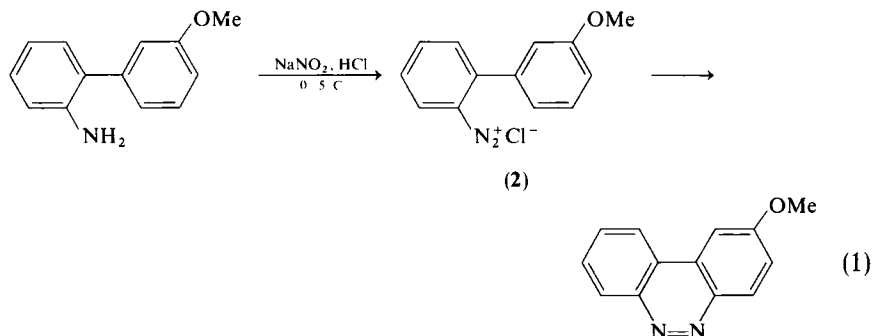
² E. Täuber, *Chem. Ber.* **24**, 3883 (1891).

³ J. C. E. Simpson, "The Chemistry of Heterocyclic Compounds, Condensed Pyridazine and Pyrazine Rings," p. 52. Wiley (Interscience), New York, 1953.

⁴ T. L. Jacobs, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 6, Ch. 5. Wiley, New York, 1957.

⁵ I. Wilson, B.Sc. Thesis, University of Bristol (1964).

⁶ J. S. Swenton, T. J. Ikeler, and B. H. Williams, *J. Am. Chem. Soc.* **92**, 3103 (1970).



compound by immediate treatment with potassium iodide, the more reactive 3',4'-dimethoxybiphenyl-2-diazonium chloride gives only 2,3-dimethoxybenzo[*c*]cinnoline under these conditions.⁷

2. 2,2'-Disubstituted Biphenyls

The most widely used method for forming the benzo[*c*]cinnoline nucleus has been the reduction of 2,2'-dinitrobiphenyl (3) and its derivatives under alkaline conditions, analogous to the bimolecular reduction of nitroarenes. As in the latter reaction, the end product is a hydrazo compound (Scheme 1), in this case the cyclic 5,6-dihydrobenzo[*c*]cinnoline (6), but this is so easily oxidized back to the fully aromatic 1 that it is not isolated unless special precautions are taken (Section IV,D). Täuber¹ originally employed 3% sodium amalgam in methanol or zinc and alkali to reduce 2,2'-dinitrobiphenyl, and these reagents have been used subsequently by other workers.⁸⁻¹⁰ Reductions using sodium sulfide^{9,10} or hydrosulfide^{9,11-14} and catalyst/hydrogen¹⁵⁻¹⁸ or catalyst/hydrazine¹⁹⁻²¹ systems have been used

⁷ J. M. Blatchly, J. F. W. McOmie, and M. L. Watts, *J. Chem. Soc.*, 5085 (1962).

⁸ J. Radell, L. Spialter, and J. Hollander, *J. Org. Chem.* **21**, 1051 (1956).

⁹ R. S. W. Braithwaite, P. F. Holt, and A. N. Hughes, *J. Chem. Soc.*, 4073 (1958).

¹⁰ J. C. Arcos, M. Arcos, and J. A. Miller, *J. Org. Chem.* **21**, 651 (1956).

¹¹ F. E. King and T. J. King, *J. Chem. Soc.*, 824 (1945).

¹² S. D. Ross, G. H. Kahan, and W. A. Leach, *J. Am. Chem. Soc.* **74**, 4122 (1952).

¹³ J. F. Corbett and P. F. Holt, *J. Chem. Soc.*, 5029 (1961).

¹⁴ J. W. Barton and J. F. Thomas, *J. Chem. Soc.*, 1265 (1964).

¹⁵ F. E. Kempter and R. N. Castle, *J. Heterocycl. Chem.* **6**, 523 (1969).

¹⁶ H. Stetter and M. Schwarz, *Chem. Ber.* **90**, 1349 (1957).

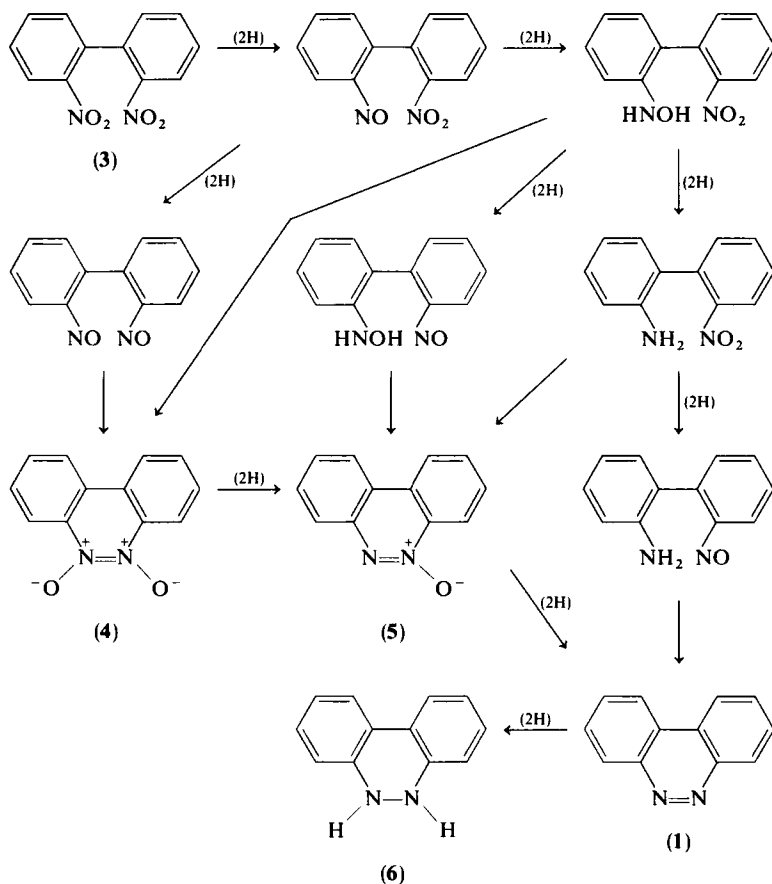
¹⁷ J. L. Everett and W. C. Ross, *J. Chem. Soc.*, 1972 (1949).

¹⁸ A. Etienne and G. Izoret, *Bull. Soc. Chim. Fr.*, 2897 (1964).

¹⁹ R. E. Moore and A. Furst, *J. Org. Chem.* **23**, 1504 (1958).

²⁰ J. W. Barton and M. A. Cockett, *J. Chem. Soc.*, 2454 (1962).

²¹ P. M. G. Bavin, *Can. J. Chem.* **36**, 238 (1958).



SCHEME 1

extensively. Electrolytic reduction^{22,23} and, in nonhydroxylic solvents, reductions with lithium aluminum hydride^{9,13,24,25} and lithium bis(2-methoxyethoxy)aluminum hydride²⁶ have given good results. The various other methods available have been discussed by Buntrock and Taylor in a review on cyclization reactions of 2,2'-disubstituted biphenyls.²⁷

²² T. Wohlfart, *J. Prakt. Chem.* **65**, 295 (1902).

²³ G. Wittig and O. Stichnoth, *Chem. Ber.* **68**, 928 (1935).

²⁴ G. M. Badger, J. H. Seidler, and B. Thomson, *J. Chem. Soc.*, 3207 (1951).

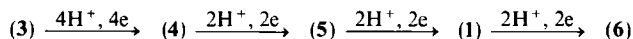
²⁵ J. F. Corbett and P. F. Holt, *J. Chem. Soc.*, 3646 (1960).

²⁶ J. F. Corbett, *J. Chem. Soc., Chem. Commun.*, 1257 (1968).

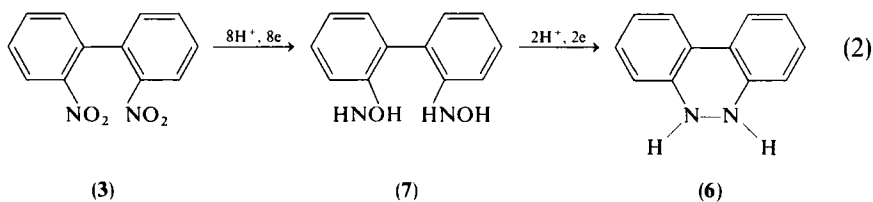
²⁷ R. E. Buntrock and E. C. Taylor, *Chem. Rev.* **68**, 209 (1968).

N,N'-Dioxides or *N*-oxides may be formed as intermediates in these reactions, depending on the stage at which N—N bond formation takes place (Scheme 1) and on the vigor of the subsequent reduction. By suitable choice of reaction conditions these may be isolated; for example, reduction of 2,2'-dinitrobiphenyl with sodium hydrosulfide gives high yields of benzo[*c*]-cinnoline 5-oxide (5),¹¹ while catalytic hydrogenation in solutions containing sodium hydroxide can be stopped at the 5,6-dioxide (4), or carried further.^{15,16,18}

Several mechanisms are possible for these cyclizations. Formation of the dioxide (4) from the unknown 2,2'-dinitrosobiphenyl would parallel the dimerization observed with acyclic nitrosoarenes, and all the other cyclization steps shown in Scheme 1 could be simple condensations, or involve radical anions, or radicals.^{28,29} Where deoxygenating reagents are used, there is also the possibility of cyclization via nitrene intermediates. It has been reported that low yields of benzo[*c*]cinnolines result from reduction of 2,2'-dinitrobiphenyls with carbon monoxide in the presence of iron pentacarbonyl³⁰ or by heating in triethyl phosphite.^{31,32} In polarographic reduction studies, Ross *et al.*^{1,2} claimed to have demonstrated the sequence:



However, another study by Emerson and Rees³³ found that benzo[*c*]-cinnoline (1) was reduced more easily than the oxides 4 and 5; thus all three are probably reduced directly to the dihydro compound 6 under these conditions. They also concluded that 2,2'-dinitrobiphenyl (3), the most easily reduced of all, is converted into 2,2'-bis(hydroxylamino)biphenyl (7) in an eight-electron step and thence into 6 [Eq. (2)]. More recent studies by cyclic voltammetry indicate that some steps may be more complex.³⁴ It has also



²⁸ G. A. Russell and E. J. Geels, *J. Am. Chem. Soc.* **87**, 122 (1965).

²⁹ F. J. Smentowsky, K. Y. Chang, J. Reynolds, and G. Kaupp, *J. Am. Chem. Soc.* **89**, 3821 (1967).

³⁰ J. E. Kmiciek, *J. Org. Chem.* **30**, 2014 (1965).

³¹ B. Coffin and R. F. Robbins, *J. Chem. Soc.*, 1252 (1965).

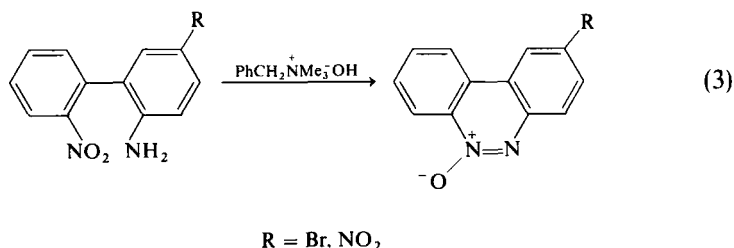
³² J. I. G. Cadogan, M. Cameron-Wood, R. K. Mackie, and R. J. G. Scarle, *J. Chem. Soc.*, 4831 (1965).

³³ T. R. Emerson and C. W. Rees, *J. Chem. Soc.*, 1923 (1962).

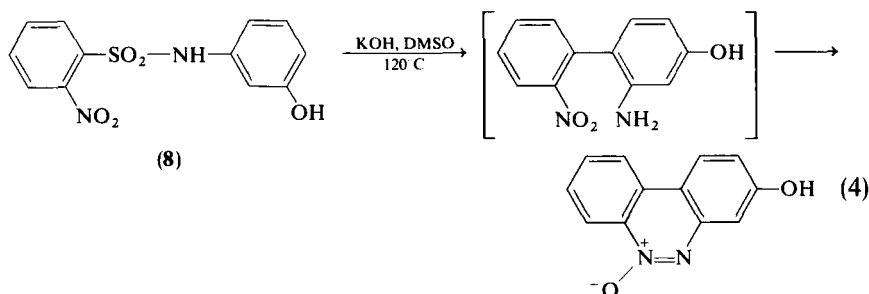
³⁴ E. Laviron and T. Lewandowska, *Bull. Soc. Chim. Fr.*, 3177 (1970).

been reported that 5,6-dihydrobenzo[*c*]cinnoline (6) is the end product in the electro chemical reduction of 2-isothiocyanato-2'-nitrobiphenyl in neutral or alkaline solution.³⁵

2-Amino-2'-nitrobiphenyls, which may be intermediates in some of the reductions, cyclize to benzo[*c*]cinnoline oxides on treatment with bases.³⁶ This reaction provides a route to certain substituted monoxides of known orientation [Eq. (3)].^{13,14}



Similarly, the base-catalyzed rearrangement of 3'-hydroxy-2-nitrobenzenesulfonanilide (8) leads to 2-amino-4-hydroxy-2'-nitrobiphenyl, which cyclizes to 3-hydroxybenzo[*c*]cinnoline 6-oxide under the reaction conditions [Eq. (4)].³⁷ When the rearrangement is carried out in aqueous solution at 250°C, the sulfite produced reduces the *N*-oxide to 3-hydroxybenzo[*c*]cinnoline.



Oxidations of 2,2'-diaminobiphenyls with sodium perborate,³⁸ phenyl iodosodiacetate,²⁰ or manganese dioxide³⁹ have given benzo[*c*]cinnolines; with hydrogen peroxide in acetic acid, cyclization is accompanied by *N*-oxidation.³⁸ These reactions, which parallel the oxidation of arylamines

³⁵ J. Hlavaty, J. Volke, and O. Manousek, *J. Electroanal. Chem. Interfacial Electrochem.* **61**, 219 (1975) [*CA* **83**, 105365 (1975)].

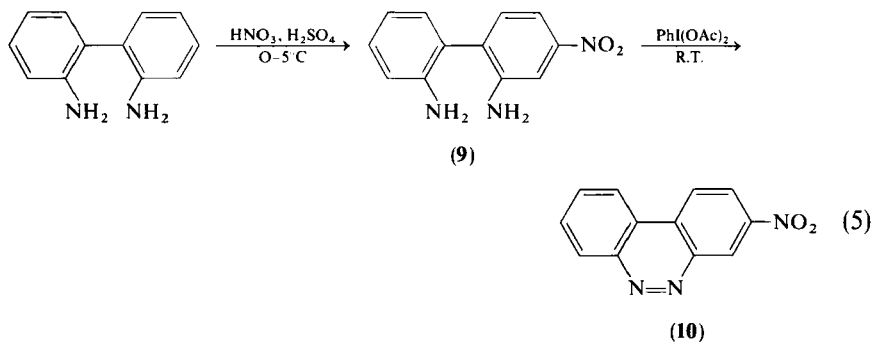
³⁶ C. W. Muth, N. Abraham, M. L. Linfield, R. B. Wotring, and E. A. Pacofsky, *J. Org. Chem.* **25**, 736 (1960).

³⁷ E. Waldau and R. Pütter, *Angew Chem., Int. Ed. Engl.* **11**, 826 (1972).

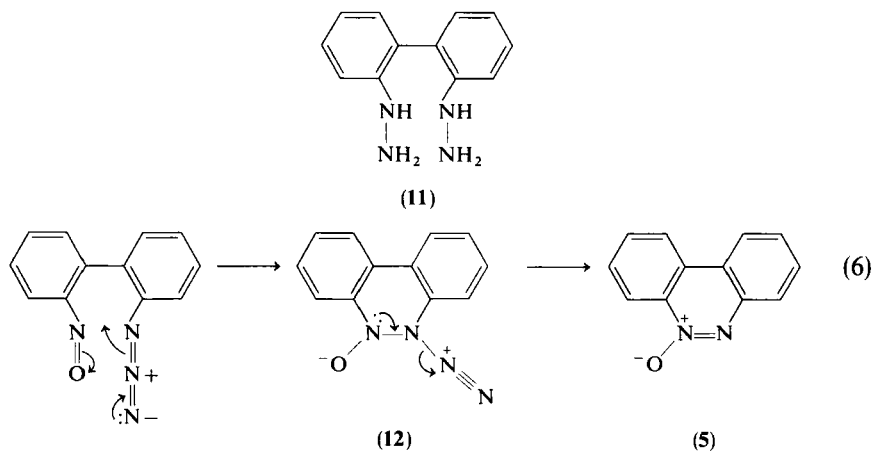
³⁸ J. F. Corbett and P. F. Holt, *J. Chem. Soc.*, 3695 (1961).

³⁹ I. Bhatnagar and M. V. George, *J. Org. Chem.* **33**, 2407 (1968).

to azo compounds, usually give poorer yields than reductions of dinitrobiaryls but are useful where other reducible substituents are present, as in the synthesis of 3-nitrobenzo[*c*]cinnoline (10) [Eq. (5)].²⁰



Benzo[*c*]cinnolines are often found as by-products of diazotization reactions of 2,2'-diaminobiphenyls. Reduction of the bisdiazonium salts from the diamines with sodium arsenite⁴⁰ or hypophosphorous acid²⁰ increases the amounts obtained, although yields are usually low; e.g., **10** is formed from **9** in 22% yield by this method.²⁰ Alternative ionic⁴¹ and homolytic⁴² mechanisms have been suggested for the process, each involving elimination of one of the diazonium groups as nitrogen. However, recent work by Rees and his co-workers has shown that at least part of the benzo[*c*]cinnolines



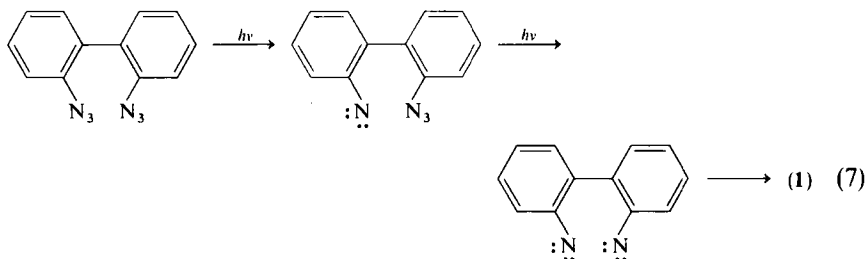
⁴⁰ R. B. Sandin and T. L. Cairns, *J. Am. Chem. Soc.* **58**, 2019 (1936).

⁴¹ K. H. Saunders and W. A. Waters, *J. Chem. Soc.*, 1154 (1946).

⁴² H. H. Hodgson, *J. Chem. Soc.*, 348 (1948).

produced derive from dibenzo[*d,f*][1,2,3]triazepines (Section II,E,2). Reduction of diazotized 2,2'-diaminobiphenyl with stannous chloride gives 2,2'-bis(hydrazino)biphenyl (**11**), which cyclizes to benzo[*c*]cinnoline on heating with aqueous hydrochloric acid at 150°C.⁴³ Nothing is known of the mechanism of the reaction except that when potassium nitrite-¹⁵N was used for the initial diazotization the results indicated that both N—N and C—N bond breaking occurred in the cyclization step.⁴⁴

Benzo[*c*]cinnoline 5-oxide is formed when 2-azido-2'-nitrosobiphenyl is heated in toluene, possibly by cyclization to the dipolar intermediate (**12**), followed by elimination of nitrogen [Eq. (6)], or via 2-nitrosobiphenyl-2'-nitrene.⁴⁵ The quantitative conversion of 2,2'-diazidobiphenyl into benzo[*c*]cinnoline by low-temperature photolysis was argued to provide evidence for a stepwise process through the azidonitrene and the dinitrene [Eq. (7)].⁴⁶



B. THE ACTION OF NITROUS ACID ON DIBENZO[*c,e*][1,2]AZABORINES

Reaction of 2-aminobiphenyl with boron trichloride followed by cyclization of the adduct gives 6-chloro-5,6-dihydrodibenzo[*c,e*][1,2]azaborine, hydrolyzed by water to the 6-hydroxy compound **13**.⁴⁷ The azaborine **13**, although its ring system remains intact during nitration⁴⁸ and acylation reactions,⁴⁹ is converted into benzo[*c*]cinnoline by diazotization in acetic acid and subsequent treatment with sodium acetate⁵⁰; the methyl ether of **13** behaves in the same way. Apparently nitrous acid brings about ring opening to the diazaboronic acid, which rearranges and then undergoes

⁴³ E. Täuber, *Chem. Ber.* **29**, 227 (1896).

⁴⁴ P. F. Holt, B. I. Hopson-Hill, and C. J. McNae, *J. Chem. Soc.*, 1404 (1961).

⁴⁵ L. A. Nieman, V. I. Maidmind, and M. M. Shemyakin, *Izv. Akad. Nauk SSSR, Ser. Khim.*, 1357 (1964) [*CA* **61**, 11991 (1964)].

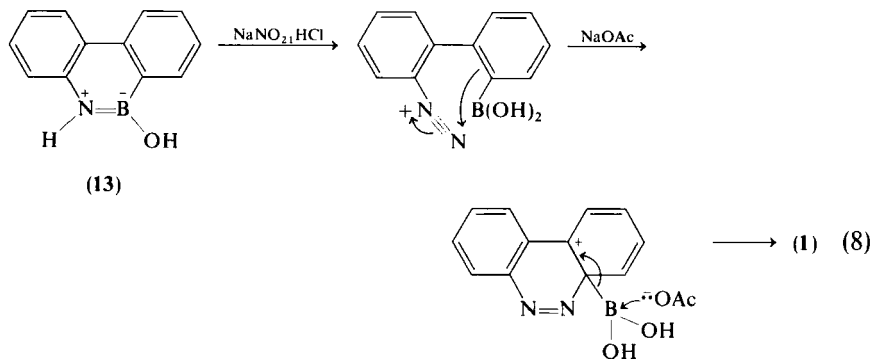
⁴⁶ A. Yabe and K. Honda, *Bull. Chem. Soc. Jpn.* **49**, 2495 (1976).

⁴⁷ M. J. S. Dewar, V. P. Kubba, and R. Pettit, *J. Chem. Soc.*, 3073 (1958).

⁴⁸ M. J. S. Dewar and V. P. Kubba, *Tetrahedron* **7**, 213 (1959).

⁴⁹ M. J. S. Dewar and V. P. Kubba, *J. Am. Chem. Soc.* **83**, 1757 (1961).

⁵⁰ M. J. S. Dewar and W. H. Poesche, *J. Chem. Soc.*, 2201 (1963).

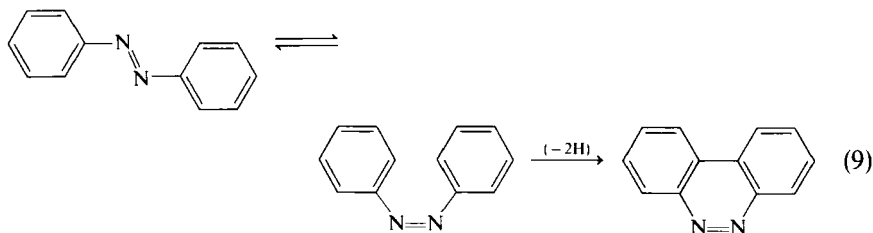


nucleophilic attack on boron [Eq. (8)]. Other polycyclic cinnolines have been prepared by this route,⁵⁰ but its scope with regard to substituents has yet to be investigated.

C. THE CYCLIZATION OF AZOBENZENES

1. Thermal

An early German patent⁵¹ first described the cyclodehydrogenation of azobenzene, 3,3'-dimethylazobenzene, and what was presumably 3,3'-dimethyl-4,4'-diaminoazobenzene to benzo[*c*]cinnolines by heating in melts of aluminum, potassium, and sodium chlorides in the presence or in the absence of air or oxidizing agents. The cyclization must proceed through



the *cis*-isomer of the azo compound and requires the removal of hydrogen at some stage [Eq. (9)], the isolation of small amounts of benzidine from the azobenzene reaction suggesting disproportionation.⁵² Some improvement in yield was claimed by using solutions of aluminum chloride in refluxing

⁵¹ A. Wolfram, E. Hausdorfer, and L. Schörnig, German Patent 513206 (1930) [*CA* **25**, 1266 (1931)].

⁵² M. A. Cockett, M.Sc. Thesis, University of Bristol (1962).

methylene dichloride⁵³ instead of melts, and the reaction was extended to azonaphthalenes; however, attempts by other workers to cyclize substituted azobenzenes have met with little success.^{52,53} The reported cyclization of 4-dimethylaminoazobenzene to 2-dimethylaminobenzo[*c*]cinnoline¹⁰ is incorrect; the product was subsequently shown to be 4,4'-bis(4-dimethylaminophenylazo)biphenyl.⁵⁴ The reaction remains obscure, and it is possible that these observations were of the photochemical cyclization, which is now well documented (see next section).

2. Photochemical

It is well known that stilbenes are converted into phenanthrenes on irradiation of solutions in organic solvents.⁵⁵ The reaction is initiated by $\pi-\pi^*$ excitation to a singlet state, which cyclizes to a dihydrophenanthrene. In the presence of dissolved oxygen, or an oxidant such as iodine, aromatization takes place. With solutions of azobenzene no such reaction occurs, but only the establishment of a *cis-trans* equilibrium, the lowest excitation in this case being $n-\pi^*$. In 1960 Lewis reported the formation of benzo[*c*]cinnoline when ethanolic solutions of azobenzene containing high concentrations of sulfuric acid were exposed to sunlight.⁵⁶ At about the same time Hugelshofer *et al.* observed benzo[*c*]cinnoline formation on ultraviolet irradiation of azobenzene in acetic acid solutions containing ferric chloride.⁵⁷

In a series of papers Lewis and co-workers have reported a comprehensive study of the photochemical reactions of azobenzenes in sulfuric acid. In the case of azobenzene itself, the products obtained were benzo[*c*]cinnoline (48%) together with benzidine (35%), and other azobenzenes gave products derived from the corresponding hydrazo compounds. The mechanism proposed is outlined in Scheme 2.⁵⁸ There is an initial rapid establishment of a *cis-trans* equilibrium of monoprotonated azobenzene,⁵⁹ with cyclization involving an excited form (14) of the *cis*-isomer, the lowest transition now being $\pi-\pi^*$. In the final step, dehydrogenation of the photocyclization product, 5,6-dihydrobenzo[*c*]cinnoline, is brought about by a second molecule of azobenzene, which is itself reduced to hydrazobenzene and

⁵³ P. F. Holt and C. W. Went, *J. Chem. Soc.*, 4099 (1963).

⁵⁴ G. E. Lewis and J. A. Reiss, *Aust. J. Chem.* **20**, 1451 (1967).

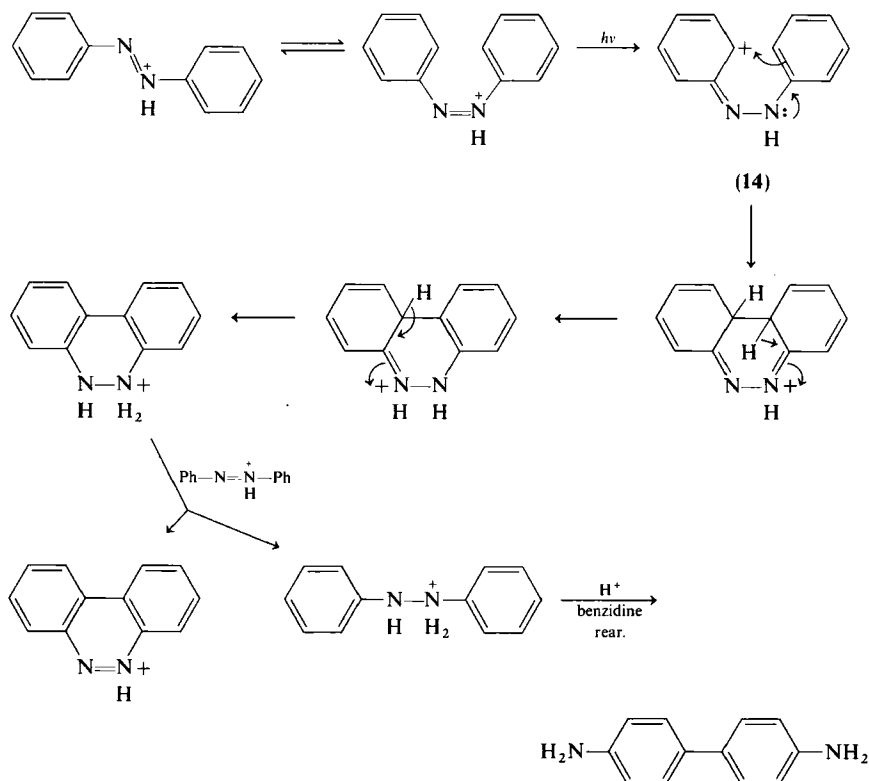
⁵⁵ E. V. Blackburn and C. J. Timmons, in "Modern Reactions in Organic Synthesis" (C. J. Timmons, ed.), Ch. 6. Van Nostrand, New York, 1970.

⁵⁶ G. E. Lewis, *Tetrahedron Lett.*, 12 (1960).

⁵⁷ P. Hugelshofer, J. Kalroda, and K. Shaffner, *Helv. Chim. Acta* **43**, 1329 (1960).

⁵⁸ G. M. Badger, R. J. Drewier, and G. E. Lewis, *Aust. J. Chem.* **19**, 643 (1966).

⁵⁹ G. E. Lewis, *J. Org. Chem.* **25**, 2193 (1960).



SCHEME 2

subsequently rearranges to benzidine under the acidic conditions. Benzo-*[c]*cinnolines have been obtained from azobenzenes with alkyl,⁶⁰ aryl,^{61,62} acetyl,⁶³ amino^{63,64} carboxyl,^{65–67} halogeno,^{65,68} methylsulfonyl,⁶⁹ and nitro⁶³ substituents, although it is found that strongly conjugating para-substituents, such as acetyl and nitro, slow the reaction. A *p*-amino substituent prevents cyclization completely, but 4-benzalaminoazobenzene

⁶⁰ G. M. Badger, R. J. Drewer, and G. E. Lewis, *Aust. J. Chem.* **16**, 1042 (1963).

⁶¹ G. M. Badger, R. J. Drewer, and G. E. Lewis, *Aust. J. Chem.* **18**, 190 (1965).

⁶² N. C. Jamieson and G. E. Lewis, *Aust. J. Chem.* **20**, 321 (1967).

⁶³ G. M. Badger, C. P. Joshua, and G. E. Lewis, *Aust. J. Chem.* **18**, 1639 (1965).

⁶⁴ G. E. Lewis and J. A. Reiss, *Aust. J. Chem.* **20**, 2217 (1967).

⁶⁵ G. M. Badger, R. J. Drewer, and G. E. Lewis, *Aust. J. Chem.* **17**, 1036 (1964).

⁶⁶ C. P. Joshua and V. N. R. Pillai, *Indian J. Chem.* **12**, 60 (1974).

⁶⁷ C. P. Joshua and V. N. R. Pillai, *Indian J. Chem.* **14B**, 525 (1976).

⁶⁸ G. E. Lewis, R. H. Prager, and R. H. M. Ross, *Aust. J. Chem.* **28**, 2459 (1975).

⁶⁹ C. P. Joshua and V. N. R. Pillai, *Indian J. Chem.* **13**, 1018 (1975).

cyclizes to 2-benzalaminobenzo[*c*]cinnoline.⁶³ In some cases yields are considerably higher than 50% based on azo compound consumed (e.g., 3-nitrobenzo[*c*]cinnoline, 90%),⁶³ probably owing to the sulfuric acid acting as oxidant so that the azo compound is not lost by reduction and rearrangement. Some benzo[*c*]cinnoline is formed with ejection of methyl, carboxyl, or halogeno substituents when 2-substituted azobenzenes are irradiated,⁶⁵ but the chief products are the 4-substituted benzo[*c*]cinnolines; migration of a methyl group has also been observed. Irradiation of 3-substituted azobenzenes gives mainly, or sometimes exclusively, 3- rather than 1-substituted benzo[*c*]cinnolines. In the case of azobenzene-3-carboxylic acid the lactone of 1-hydroxybenzo[*c*]cinnoline-10-carboxylic acid was obtained in addition to benzo[*c*]cinnoline-3-carboxylic acid.⁶⁵

It has been shown that Lewis acids may replace sulfuric acid in the photocyclization, so that the reactions may be conducted in acetic acid⁷⁰ or non-protic solvents.⁷¹ Thus, the photocyclization of azobenzene in acetic acid containing ferric chloride, reported in 1960, falls into this category, the ferric chloride acting both as a Lewis acid and an oxidant. In certain cases it appears that hydrogen bonding to the azo group is sufficient to raise the energy of the $n-\pi^*$ transition above that of the $\pi-\pi^*$, and so facilitate photocyclization in the absence of a Lewis acid. Extended irradiations of azobenzene-2-carboxylic and -2,2'-dicarboxylic acids in 1,2-dichloroethane have given low yields of the corresponding benzo[*c*]cinnoline carboxylic acids, whereas the methyl esters do not cyclize.^{66,72}

D. THE PHOTOCHEMICAL BRIDGING AND SUBSEQUENT RING CLEAVAGE OF TETRAZOLIUM SALTS

When 2,3,5-triphenyltetrazolium chloride (**16**), formed by oxidation of the formazan **15**, is exposed to sunlight or ultraviolet light in dilute solution, it disproportionates to the bridged tetrazolium salt **17** and the formazan (Scheme 3).^{73,74} By carrying out the irradiation in the presence of dilute nitric acid the formazan is reoxidized to the tetrazolium salt (**16**), so that high yields of the bridged salt result.⁷⁵ Reduction of **17** gives first the stable,

⁷⁰ G. E. Lewis and R. J. Mayfield, *Aust. J. Chem.* **19**, 1445 (1966).

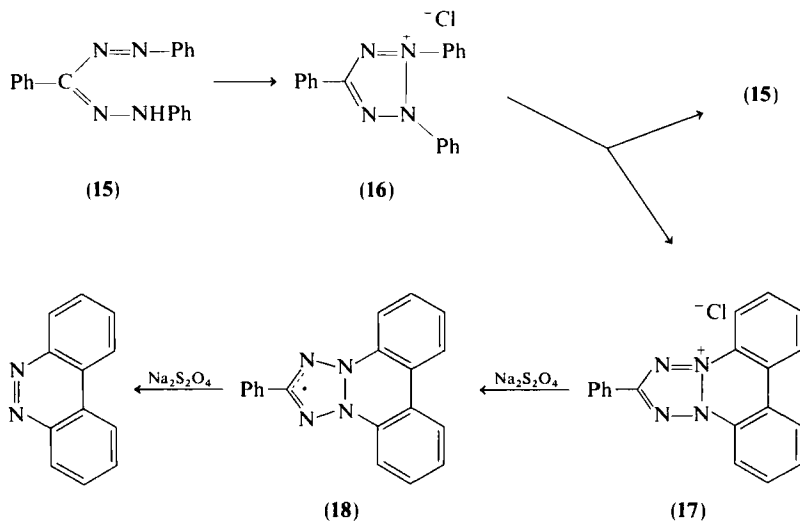
⁷¹ C. P. Joshua and V. N. R. Pillai, *Tetrahedron Lett.*, 2493 (1972).

⁷² C. P. Joshua and V. N. R. Pillai, *Tetrahedron Lett.*, 3559 (1973).

⁷³ F. Weygand and I. Frank, *Z. Naturforsch., Teil B* **3**, 377 (1948).

⁷⁴ I. Hausser, D. Jerchel, and R. Kuhn, *Chem. Ber.* **82**, 195 (1949).

⁷⁵ D. Jerchel and H. Fischer, *Justus Liebigs Ann. Chem.* **590**, 216 (1954).



SCHEME 3

olive-green radical **18**,⁷⁶ which is further reduced to benzo[*c*]cinnoline by cleavage of the tetrazole ring.^{73,75} Benzo[*c*]cinnoline derivatives with alkoxyl, carboxyl, and halogen substituents have been obtained using this sequence, but triphenyltetrazolium salts bearing *p*-nitro groups failed to cyclodehydrogenate.⁷⁵

E. RING CONTRACTION OF OTHER HETEROCYCLES

1. Diazepines

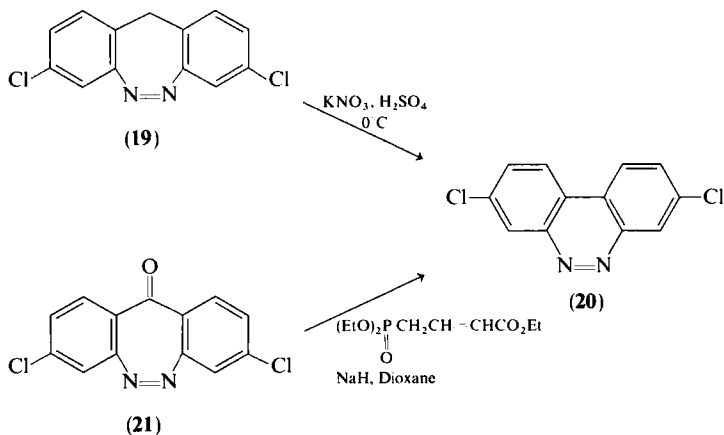
Two ring-contractions of dibenzo[*c,f*][1,2]diazepine derivatives to a benzo[*c*]cinnoline have been reported. Attempted nitration of 3,8-dichloro-(11H)-dibenzo[*c,f*][1,2]diazepine (**19**) in sulfuric acid⁷⁷ gave 3,8-dichlorobenzo[*c*]cinnoline (**20**), and the same compound was obtained when the corresponding diazepinone (**21**) was allowed to react with ethyl 4-(diethoxyphosphinyl)crotonate.⁷⁸

The mechanisms of these extrusions are unknown, and attempts to vary the reaction conditions gave negative results.

⁷⁶ R. Kuhn and D. Jerchel, *Justus Liebigs Ann. Chem.* **578**, 1 (1952).

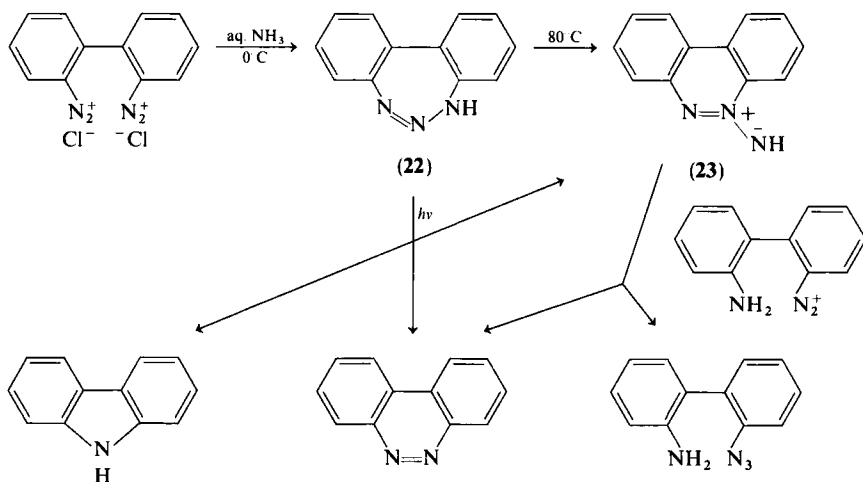
⁷⁷ R. J. Dubois and F. D. Popp, *J. Heterocycl. Chem.* **6**, 113 (1969).

⁷⁸ R. J. Dubois and F. D. Popp, *J. Chem. Soc., Chem. Commun.*, 675 (1968).



2. Triazepines

When 2,2'-diaminobiphenyl is bis-diazotized at 0°C (see also Section II,A,2) and the solution is neutralized with ammonia at that temperature, dibenzo[*d,f*][1,2,3]triazepine (22) precipitates as a yellow solid (Scheme 4).⁷⁹ Although moderately stable, 22 rearranges quantitatively to benzo[*c*]-cinnoline-5-imide (23) on heating in benzene.⁸⁰ The imide (23) is also the



SCHEME 4

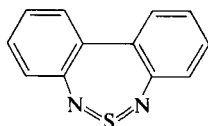
⁷⁹ S. F. Gait, M. E. Peek, C. W. Rees, and R. C. Storr, *J.C.S. Perkin I*, 1248 (1974).

⁸⁰ S. F. Gait, M. E. Peek, C. W. Rees, and R. C. Storr, *J.C.S. Perkin I*, 19 (1975).

main product from aprotic diazotization of 2,2'-diaminobiphenyl in refluxing benzene, the other product being benzo[*c*]cinnoline. The latter probably arises by imide transfer from **23** to the 2-aminobiphenyl-2'-diazonium ion which is thereby converted into 2-amino-2'-azidobiphenyl. Photolysis of **22** in acetonitrile gives the imide (**23**), together with benzo[*c*]cinnoline and small amounts of carbazole. When benzophenone is used as a sensitizer more benzo[*c*]cinnoline is obtained at the expense of **23**. The corresponding reactions of certain methyl- and methoxy-substituted triazepines have been described.⁸⁰

3. *Thiadiazepines*

The reaction of 2,2'-diaminobiphenyl with thionyl chloride in refluxing toluene gives dibenzo[*c,e*][1,2,7]thiadiazepine (**24**). This compound is ther-



(24)

mally unstable and on heating is converted into benzo[*c*]cinnoline by extrusion of sulfur, the latter being formed directly when the original reaction is carried out in boiling xylene.⁸¹

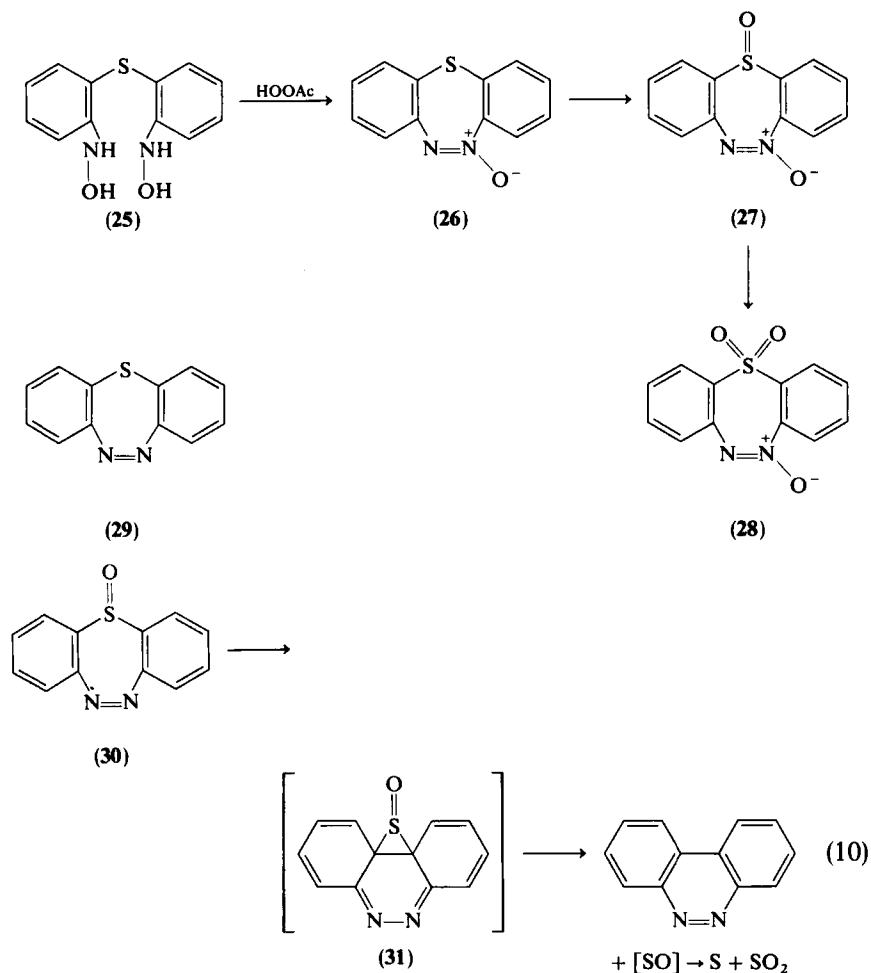
Reduction of di(2-nitrophenyl)sulfide with zinc and sodium acetate in isopropanol gives the dihydroxylamino compound **25**,⁸² which may be oxidatively cyclized to dibenzo[*b,f*][1,4,5]thiadiazepine-5-oxide (**26**) with peracetic acid. With an excess of reagent, **26** is further oxidized to the 5,11-dioxide (**27**) and finally to the 5,11,11-trioxide (**28**). By other reduction-oxidation reactions of **26**, **27**, and **28**, the parent thiadiazepine (**29**) and other derivatives of the ring system in various oxidation levels at nitrogen have been prepared.⁸³ It is found that the derivatives of **29** having a sulfide or sulfone bridge are thermally stable, whereas the sulfoxide (**30**) decomposes readily at ambient temperatures into benzo[*c*]cinnoline, sulfur, and sulfur dioxide. Trapping experiments indicate that **30** decomposes by extrusion of sulfur monoxide, probably following a disrotatory cyclization to the intermediate **31** [Eq. (10)].⁸⁴ A rate study of the decomposition in toluene

⁸¹ G. R. Collins, Ph.D. Thesis, Indiana University (1965).

⁸² H. H. Szmant and Y. L. Chow, *J. Am. Chem. Soc.* **79**, 4382 (1957).

⁸³ H. H. Szmant and Y. L. Chow, *J. Org. Chem.* **36**, 2887 (1971).

⁸⁴ Y. L. Chow, J. N. S. Tam, J. E. Blier, and H. H. Szmant, *J. Chem. Soc., Chem. Commun.*, 1604 (1970).

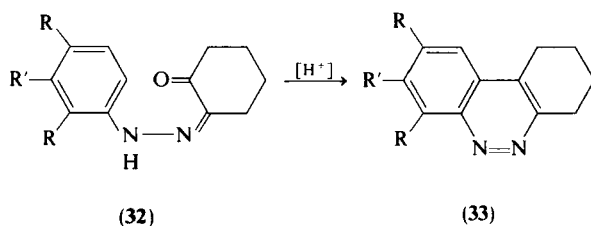


at 65°C has given an approximate value of 26 kcal/mole for the activation energy of the process. The dioxide **27** also decomposes in solution at 100°C to a mixture of benzo[c]cinnoline and its 5-oxide; presumably some of the latter is deoxygenated by the sulfur oxides formed.

F. MISCELLANEOUS REACTIONS

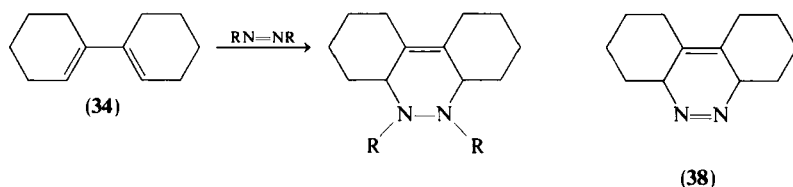
Several reactions leading to reduced benzo[c]cinnolines have been reported. Cyclohexane-1,2-dione monoarylhydrazones (**32**) have been dehy-

drated to 1,2,3,4-tetrahydrobenzo[*c*]cinnolines (**33**) in sulfuric or phosphoric acids.⁸⁵⁻⁸⁸ Only poor yields of the cinnolines **33** ($R = R' = H$)⁸⁵⁻⁸⁷ and



33 ($R = H$; $R' = OMe$) were obtained from the corresponding hydrazones; in the former case the main product of the reaction was 1,2,3,4-tetrahydrocarbazol-1-one.⁸⁶ Better yields were reported for the cyclization of **32** ($R = Me$; $R' = H$) and for the cyclohexane-1,2-dione mononaphthylhydrazones,⁸⁷ the products from the last two being dehydrogenated to the fully aromatic naphtho[*c*]cinnolines.

Cycloadditions of 1,1'-bicyclohexenyl (**34**) with acylazo compounds have given high yields of the tetrahydropyridazines **35** and **36**.^{89,90} No attempts have been made to aromatize such compounds, but it is found that alkaline hydrolysis of **36** is accompanied by decarboxylation to the unstable **37**, which is oxidized by air back to 1,1'-bicyclohexenyl with loss of nitrogen, presumably via the dihydropyridazine **38**.⁹⁰



(35) $R = COAp$

(36) $R = CO_2Et$

(37) $R = H$

⁸⁵ B. P. Moore, *Nature (London)* **163**, 918 (1949).

⁸⁶ R. A. Soutter and M. Tomlinson, *J. Chem. Soc.*, 4256 (1961).

⁸⁷ R. S. W. Braithwaite and G. K. Robinson, *J. Chem. Soc.*, 3671 (1962).

⁸⁸ M. J. M. Pollmann, H. R. Rens, U. K. Pandit, and H. O. Huisman, *Rec. Trav. Chim. Pays-Bas* **89**, 929 (1970).

⁸⁹ Y. S. Shabarov, N. I. Vasilev, I. S. Levina, and R. Y. Levina, *J. Gen. Chem. USSR* **32**, 2806 (1962).

⁹⁰ B. T. Gillis and P. E. Beck, *J. Org. Chem.* **28**, 3177 (1963).

III. Physical Properties of Benzo[c]cinnolines. Spectra

A. BENZO[c]CINNOLINE: PHYSICAL PROPERTIES AND BOND STRUCTURE

Benzo[c]cinnoline is a weakly basic compound (Section IV,A), crystallizing from water or cyclohexane in yellow, monoclinic needles of m.p. 156°C. It is very soluble in alcohols, ether, etc. An X-ray crystallographic study⁹¹ has shown the molecule to be only approximately planar, forming molecular pairs with opposed dipoles in the solid state; dimerization also takes place in solution at low temperature.⁹² It is found that bonds 1—2, 3—4, 7—8, and 9—10 are shorter than the others of the benzene rings, indicating a degree of bond fixation with **1** as the "preferred" Kekulé structure.

B. ULTRAVIOLET SPECTRA

The ultraviolet spectrum of benzo[c]cinnoline in *n*-hexane shows four band systems centred at approximately 250, 300, 350, and 400 nm. The first three of these are π — π^* bands, corresponding to those in the spectrum of phenanthrene, while the long-wavelength band, of low intensity, is due to an n — π^* transition.⁹³ In hydroxylic solvents this last band moves to shorter wavelengths and becomes obscured. Substituent effects, and those due to protonation and to *N*-oxidation, have been discussed in a series of papers by Holt and co-workers.^{13,94,95}

C. NUCLEAR MAGNETIC RESONANCE SPECTRA

The proton magnetic resonance spectrum of benzo[c]cinnoline in deuteriochloroform shows three multiplets at τ 1.36, τ 1.57, and τ 2.18 due to protons H_{4,7}, H_{1,10}, and H_{2,3,8,9}, respectively. In hexadeuteriobenzene the last two multiplets show a marked shift to higher field whereas the first is unaffected. When Martin *et al.*⁹⁶ first recorded the spectrum they made the

⁹¹ H. Van Der Meer, *Acta Crystallogr., Sect B* **28**, 367 (1972).

⁹² D. N. de Vries Reilingh, R. P. Rettschnick, and G. J. Hoytink, *J. Chem. Phys.* **54**, 2722 (1971).

⁹³ G. M. Badger and I. S. Walker, *J. Chem. Soc.*, 122 (1956).

⁹⁴ J. F. Corbett, P. F. Holt, A. N. Hughes, and M. Vickery, *J. Chem. Soc.*, 1812 (1962).

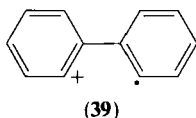
⁹⁵ P. F. Holt and R. Oakland, *J. Chem. Soc.*, 1306 (1966).

⁹⁶ R. H. Martin, N. Defay, F. Geerts-Evrard, and D. Bogaert-Verhoogen, *Tetrahedron, Suppl.* **8**, Part 1, 181 (1966).

opposite assignments for the two lowfield multiplets. In recent studies Kooti and Nixon⁹⁷ have assigned the multiplets as $H_{4,7}$, $H_{3,8}$, and $H_{1,2,9,10}$, respectively; however, other workers^{98,99} have assumed the assignments given here, and these have been confirmed by analysis of the spectra of the monobromobenzo[c]cinnolines.¹⁰⁰ Estimates of the various coupling constants have been made by comparison with computer-simulated spectra.⁹⁹ The ^{13}C magnetic resonance spectrum of benzo[c]cinnoline has been examined,^{97,101} but complete assignments have yet to be made.

D. MASS SPECTRA

The mass spectrum of benzo[c]cinnoline¹⁰² shows a main initial loss of N_2 from the molecular ion (m/e 180) to give a biphenylene radical ion (m/e 152; base peak), which probably has the open structure **39**, as postulated



for the parent ion of biphenylene.^{103,104} Further fragmentation follows that observed for biphenylene. With benzo[c]cinnoline 5-oxide¹⁰⁵ initial loss of NO is more important than loss of O, as shown by some *N*-oxides. Benzo[c]cinnoline 5-imide⁸⁰ shows a ready loss of NH to give the base peak (m/e 180). From the mass spectra of *C*-monosubstituted benzo[c]-cinnolines examined so far,¹⁰² it appears that when substituents such as Me, Cl, NH_2 , NMe_2 , or CO_2H are present in positions 1-, 2-, or 3-, then loss of N_2 is the main initial process. Other substituents, such as OMe, OEt, NEt_2 , CO_2Me , and CO_2Et , undergo fragmentation prior to N_2 loss from the nucleus. The behavior of 4-substituted derivatives is not in line with these findings, as the ring nitrogen atom at position 5 is often involved in the fragmentation processes.

⁹⁷ M. Kooti and J. F. Nixon, *J. Organomet. Chem.* **105**, 217 (1976).

⁹⁸ R. P. Bennett, *Inorg. Chem.* **9**, 2184 (1970).

⁹⁹ P. J. Abbot, R. M. Acheson, M. W. Foxton, N. R. Raulins, and G. E. Robinson, *J.C.S. Perkin I*, 2182 (1972).

¹⁰⁰ J. W. Barton and D. J. Lapham, unpublished work.

¹⁰¹ S. R. Challand, S. F. Gait, C. W. Rees, and R. C. Storr, *J.C.S. Perkin I*, 26 (1975).

¹⁰² J. H. Bowie, G. E. Lewis, and J. A. Reiss, *Aust. J. Chem.* **21**, 1233 (1968).

¹⁰³ D. F. Lindow and L. Friedman, *J. Am. Chem. Soc.* **89**, 1271 (1967).

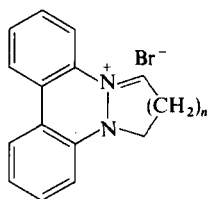
¹⁰⁴ L. Friedman and D. F. Lindow, *J. Am. Chem. Soc.* **90**, 2324 (1968).

¹⁰⁵ J. H. Bowie, R. G. Cooks, N. C. Jamieson, and G. E. Lewis, *Aust. J. Chem.* **20**, 2545 (1967).

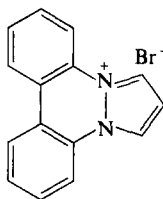
IV. Chemistry of Benzo[c]cinnoline

A. PROTONATION AND QUATERNIZATION. *N*-YLIDES

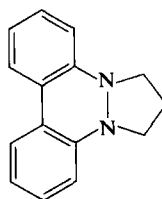
Benzo[c]cinnoline is a weak base with a pK_a of 2.2 in water and 1.6 in 50% aqueous ethanol.¹⁰⁶ Cryoscopic measurements show that it is diprotonated to some extent in 100% sulfuric acid.¹⁰⁷ Well-defined quaternary salts result from heating benzo[c]cinnoline with alkyl halides and sulfates.^{22,108} These are reported to decompose on treatment with ammonia, regenerating benzo[c]cinnoline,¹⁰⁸ but apparently nucleophilic displacements of halogen by amines have been carried out on certain highly substituted examples in the synthesis of cationic dyestuffs.¹⁰⁹ Quaternizations of benzo[c]cinnoline with α,ω -dibromo-propane and -butane are accompanied by hydrogen bromide elimination to give the cyclic iminium salts **40** and **41**.^{110,111} When **40** is dehydrogenated, or merely refluxed in ethanol,



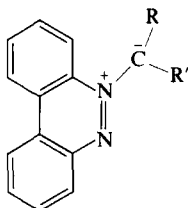
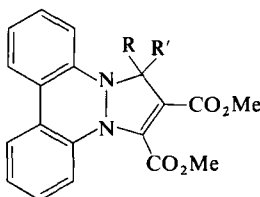
(40) $n = 1$
(41) $n = 2$



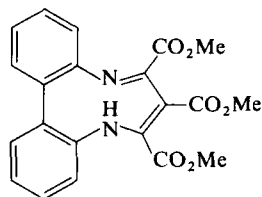
(42)



(43)

(44) $R = H$; $R' = CO_2Me$ (45) $R = R' = CO_2Et$ (46) $R = R' = CN$ (47) $R = H$, $R' = COPh$ 

(48)



(49)

¹⁰⁶ P. H. Gore and J. N. Phillips, *Nature (London)* **163**, 690 (1949).

¹⁰⁷ R. H. Altiparmakian and R. S. W. Braithwaite, *J. Chem. Soc. B*, 1112 (1967).

¹⁰⁸ F. Ullmann and P. Dieterle, *Chem. Ber.* **37**, 23 (1904).

¹⁰⁹ W. Kalk and K. H. Schuendehuetten, German Patent 2,041,689 (1972) [*CA* **77**, P36390 (1972)].

¹¹⁰ D. G. Farnum, R. J. Alaimo, and J. M. Dunston, *J. Org. Chem.* **32**, 1130 (1967).

¹¹¹ E. Carp, M. Dorneanu, and I. Zugravescu, *An. Stiint. Univ. "Al. I. Cuza" Iasi, Sect. 1c* **14**, 169 (1968).

it is converted into the fully aromatic benzo[*c*]pyridazo[1,2-*a*]cinnolinium salt **42**, while borohydride reduction leads to **43**.¹¹⁰

Ylides **44–47** result from mild base treatment of the corresponding quaternary salts^{110,112,113}; others have been obtained in ring-opening reactions of the cycloaddition products of benzo[*c*]cinnoline *N*-oxides and *N*-imides with acetylenic esters and dicyanoacetylene (Sections IV,E and F). Whereas the dicyanoylide (**46**) is unreactive,¹¹² the others undergo cycloaddition reactions with dimethyl acetylenedicarboxylate to give the pyrazole derivatives (**48**).^{110,112,113} It has been reported recently that treatment of **48** (R = H; R' = CO₂Me) with lithium methoxide gives, after acidification, the ring-opened product **49**, the first example of a derivative of the aromatic 10 π -electron 1,5-diazonin system.¹¹⁴

B. ELECTROPHILIC SUBSTITUTION

Theoretical studies of the neutral^{115,116} and monoprotonated^{117,118} benzo[*c*]cinnoline molecules have predicted that position 1 should be the most reactive in electrophilic substitution, there being some doubt as to whether the next most reactive position would be 3 or 4. The nitration of benzo[*c*]cinnoline in sulfuric acid has been well investigated [Eq. (11)]. Although some early studies gave conflicting results,¹⁰ it is now established that 1- and 4-nitrobenzo[*c*]cinnolines are formed in the ratio of ca. 4:1 at temperatures between 0° and 100°C.^{20,118,119} This nitration pattern parallels that of cinnoline, which is nitrated in positions 5 and 8 under similar conditions. With a large excess of "mixed acid" at room temperature, 1-nitrobenzo[*c*]cinnoline is nitrated further to give the 1,10-dinitro derivative, the 4-nitro isomer being unaffected.¹²⁰ Under similar conditions 1,10-dimethylbenzo[*c*]cinnoline is nitrated in positions 4 and 7.¹²¹ Nitrations of 3-methyl-, 2,9-dimethyl-, and 3,8-dimethylbenzo[*c*]cinnolines apparently give products in keeping with the above findings, but the structures of the products were based on ultraviolet spectroscopic evidence only.¹¹⁸

¹¹² E. Carp, M. Dorneanu, and I. Zugravescu, *Rev. Roum. Chim.* **19**, 1507 (1974).

¹¹³ S. F. Gait, M. J. Rance, C. W. Rees, R. W. Stephenson, and R. C. Storr, *J.C.S. Perkin I*, 556 (1975).

¹¹⁴ D. G. Farnum and K. Rashid, *J. Org. Chem.* **42**, 573 (1977).

¹¹⁵ A. Pullman, *Rev. Sci.* **86**, 219 (1948).

¹¹⁶ H. C. Longuet-Higgins and C. A. Coulson, *J. Chem. Soc.*, 971 (1949).

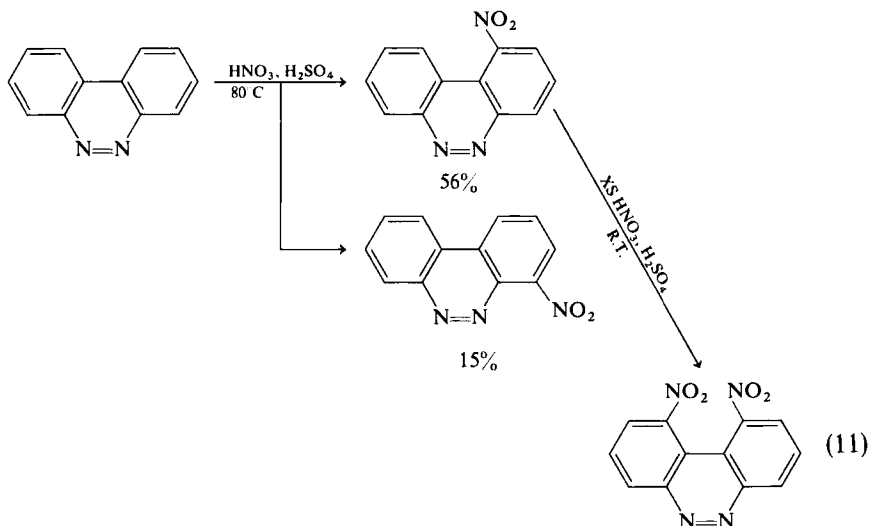
¹¹⁷ M. J. S. Dewar and P. M. Maitlis, *J. Chem. Soc.*, 2521 (1957).

¹¹⁸ J. F. Corbett, P. F. Holt, and M. L. Vickery, *J. Chem. Soc.*, 4860 (1962).

¹¹⁹ W. T. Smith and P. R. Ruby, *J. Am. Chem. Soc.* **76**, 5807 (1954).

¹²⁰ J. F. Corbett, P. F. Holt, and M. L. Vickery, *J. Chem. Soc.*, 4384 (1962).

¹²¹ W. Theilacker and F. Baxmann, *Justus Liebigs Ann. Chem.* **581**, 117 (1953).



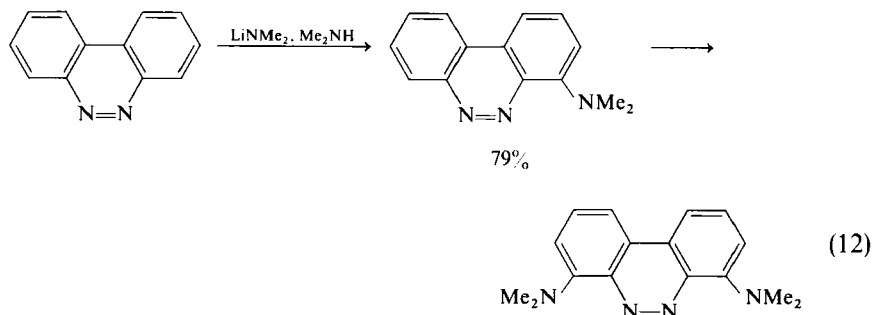
Benzo[*c*]cinnoline forms molecular complexes with halogens in organic solvents; thus attempts to brominate it with molecular bromine have been unsuccessful.^{13,119} Using a source of "positive" bromine, bromine/silver sulfate in sulfuric acid, Corbett and Holt found that reaction occurred at room temperature to give 27% of a monobromo and 4% of a dibromo derivative.¹³ These compounds were at first identified as 1-bromo- and 1,4-dibromo-(or 1,7-dibromo-)benzo[*c*]cinnolines, but the former was subsequently shown to be the 4 isomer.^{14,95} A reinvestigation of the reaction¹⁰⁰ has shown that both 1- and 4-bromobenzo[*c*]cinnolines are primary products, formed in the ratio of ca. 2.3:1 at room temperature. The lower isomer ratio as compared with nitration in sulfuric acid probably reflects the greater steric demand of the attacking species. The dibromo compound formed is the 1,4-isomer. The formation of the octachloro derivative by chlorination of benzo[*c*]cinnoline in the presence of aluminum chloride has been mentioned,¹²² but no details are available.

C. NUCLEOPHILIC SUBSTITUTION

The only recorded nucleophilic substitutions of benzo[*c*]cinnoline are with lithium dialkylamides. The reaction with lithium dimethylamide in dimethylamine gives 4-dimethylaminobenzo[*c*]cinnoline,^{68,123} further at-

¹²² J. A. H. McBride, *J. Chem. Soc., Chem. Commun.*, 1219 (1972).

¹²³ G. E. Lewis and J. A. Reiss, *Aust. J. Chem.* **21**, 1043 (1968).



tack taking place at position 7 [Eq. (12)]. Halogenobenzo[*c*]cinnolines are also attacked at these positions by lithium dimethylamide, but complex mixtures result from accompanying aryne reactions (Section V,E).

D. ADDITION REACTIONS

Hydrogenation of benzo[*c*]cinnoline with active Raney nickel catalysts⁸ brings about ring opening to 2,2'-diaminobiphenyl, as does reduction with hydrazine in the presence of Raney nickel.¹⁹ Mild catalytic reduction with a palladium/alumina catalyst at atmospheric pressure,¹²⁴ or chemical reduction with zinc dust in acidic¹²⁵ or alkaline¹²⁶ solution gives 5,6-dihydrobenzo[*c*]cinnoline (**6**), isolable as the monohydrochloride. The free base is unstable, being oxidized back to the fully aromatic system extremely easily; however, the isolation of a peroxide has been reported.¹²⁴ Exposure of a solution of benzo[*c*]cinnoline in acidified isopropanol to visible light is reported to give first the dihydro compound (**6**), then 2,2'-diaminobiphenyl. When ultraviolet light is used, ammonia is evolved, presumably from **6**, and the main product is carbazole.¹²⁷ Stable mono- and diacyl derivatives of **6** have been prepared by reaction with acid chlorides, anhydrides, and esters,^{124,125,128,129} and some cyclic ones show physiological activity and have been patented^{130,131} as useful in the treatment of rheumatic ailments.

¹²⁴ A. Etienne and R. Piat, *Bull. Soc. Chim. Fr.*, 292 (1962).

¹²⁵ H. Kuhne and H. Erlenmeyer, *Helv. Chim. Acta* **38**, 531 (1955).

¹²⁶ H. Duval, *Bull. Soc. Chim. Fr.*, 485 (1910).

¹²⁷ H. Inoue and Y. Matsuda, *Chem. Lett.* **8**, 713 (1972).

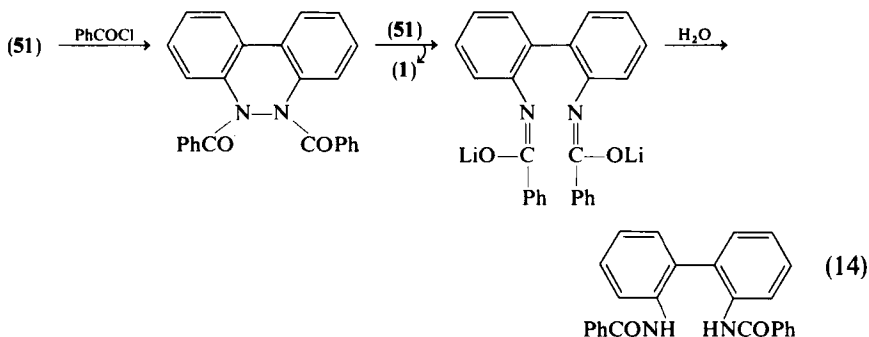
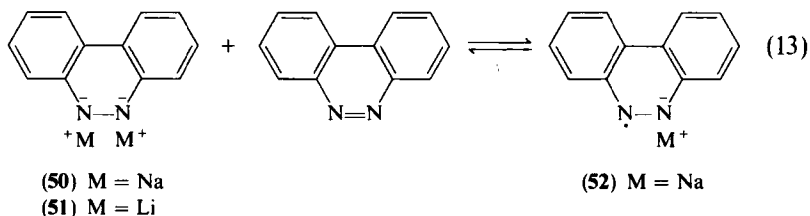
¹²⁸ G. Wittig, M. A. Jesaitis, and M. Glos, *Justus Liebigs Ann. Chem.* **577**, 1 (1952).

¹²⁹ G. Wittig and A. Schumacher, *Chem. Ber.* **88**, 234 (1955).

¹³⁰ M. Matter, U.S. Patent 2,778,829 (1957) [*CA* **51**, 11397 (1957)].

¹³¹ H. Erlenmeyer, Swiss Patents 330,123; 331,374; 331,699 (1958) [*CA* **52**, P6269 (1958)]; British Patent 794,775 (1958) [*CA* **52**, P418 (1958)].

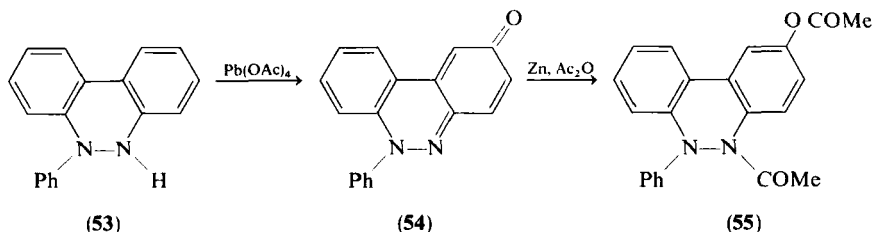
In ether solutions in the absence of air, benzo[*c*]cinnoline forms adducts with alkali metals containing two atoms of the metal. These give solutions of **6** on treatment with benzoic acid or other source of protons.¹²⁸ When one equivalent of benzo[*c*]cinnoline is added to the violet solution of the disodium derivative (**50**), an equilibrium is set up and the dark green sodium derivative of the radical anion (**52**) precipitates [Eq. (13)].¹²⁹ Reaction of the dilithium adduct (**51**) with one equivalent of benzoyl chloride results in disproportionation into benzo[*c*]cinnoline and, after hydrolysis, 2,2'-dibenzamidobiphenyl [Eq. (14)].¹²⁸ Methylation of the dilithium derivative



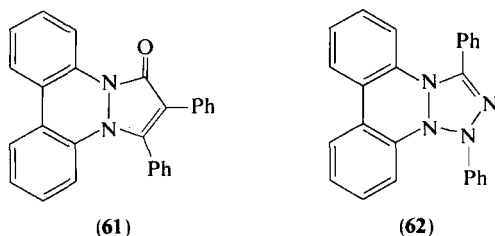
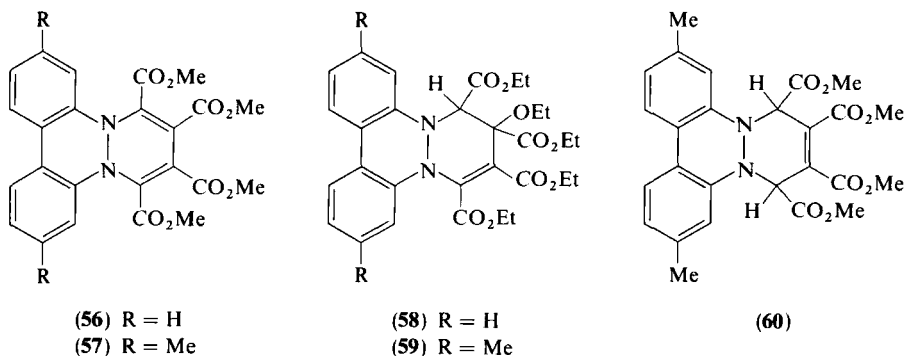
of 1,10-dimethylbenzo[*c*]cinnoline with dimethyl sulfate gives 5,6-dihydro-1,5,6,10-tetramethylbenzo[*c*]cinnoline. This undergoes oxidative demethylation under very mild conditions to regenerate 1,10-dimethylbenzo[*c*]cinnoline, and it is reduced by zinc and dilute acid to 2,2'-bis(methylamino)-6,6'-dimethylbiphenyl.²³

Phenyllithium adds to the N=N bond of benzo[*c*]cinnoline giving, on work-up, the air-sensitive, 5,6-dihydro-5-phenylbenzo[*c*]cinnoline (**53**). In an attempt to generate the radical corresponding to triphenylhydrazyl from **53**, Wittig and Schumacher¹²⁹ found that oxidation with silver oxide or lead tetraacetate produced instead the quinonimine **54**, analogous to the product formed by methylating 2-hydroxybenzo[*c*]cinnoline (Section V,D). On reductive acetylation, the quinonimine is converted into the 5,6-dihydro

derivative **55**. Similar attempts to generate the monoacyl radicals by oxidation of 5-acyl-5,6-dihydrobenzo[*c*]cinnolines resulted in disproportionation into benzo[*c*]cinnoline and the corresponding 5,6-diacyl-5,6-dihydrobenzo[*c*]cinnolines.¹²⁹



Thermal cycloaddition reactions of benzo[*c*]cinnoline with butadiene and isoprene are reported to give only small yields of adducts in various solvents.¹¹¹ Reactions of **1** and its 3,8-dimethyl derivative with dimethyl acetylenedicarboxylate at room temperature give the 1:2 adducts **56** and **57** via a stepwise process involving dipolar intermediates (see also Sections IV,A and F).^{99,112,132} The corresponding reactions of the diethyl ester in



ethanol give adducts containing one molecule of solvent for which structures **58** and **59** were proposed, the difference in behavior being attributed to

¹³² A. N. Hughes and T. Monkoltananont, *Chem. Ind. (London)*, 662 (1967).

steric factors. Hydrolysis of **56** regenerates benzo[*c*]cinnoline, and catalytic reduction of **57** gives what is thought to be one of the stereoisomers of **60**. Other cycloadditions of benzo[*c*]cinnoline reported are those with diphenylcyclopropenone and with diphenylnitrilimine to give the pyrazolone **61**¹³³ and a compound to which the dihydrotetrazole structure **62** was assigned.¹¹¹

E. OXIDATION. BENZO[*c*]CINNOLINE *N*-OXIDES

The benzo[*c*]cinnoline ring system is resistant to oxidation by chromic acid, but is oxidized to pyridazinetetracarboxylic acid by alkaline permanganate.¹³⁴ Benzo[*c*]cinnoline has been oxidized to the 5-oxide¹³⁵ with hydrogen peroxide in acetic acid at 0°C, and further to the 5,6-dioxide at 110°–120°C.¹³⁶ The *N*-oxidation of various other derivatives has been reported,^{13,14,20,135,137} although the main method for the preparation of *N*-oxides has been by the reduction of 2,2'-dinitrobiphenyls (Section II,A,2). In the case of unsymmetrically substituted compounds, both of the above methods usually give mixtures of 5- and 6-oxides. Selectivity is occasionally observed, thus 4-bromobenzo[*c*]cinnoline is oxidized to the 6-oxide,¹⁴ presumably owing to steric factors. Benzo[*c*]cinnoline oxides of known orientation have been obtained by the cyclization of 2-amino-2'-nitrobiphenyl derivatives (Section II,A,2).

Benzo[*c*]cinnoline-5,6-dioxide is a colorless, high-melting (243°C), non-basic compound, sparingly soluble in organic solvents. There has been discussion of spectroscopic evidence as to whether it has a di-*N*-oxide or a nitroso-dimer type structure,^{12,137,138} but there has been little investigation of its chemistry and there appears to be no chemical evidence for its behaving as 2,2'-dinitrosobiphenyl; i.e., it shows no nitroso group reactions.

Benzo[*c*]cinnoline-5-oxide is a colorless compound, m.p. 139°C, which is less basic than benzo[*c*]cinnoline, being precipitated on dilution of its solution in hydrochloric acid. Of its reactions, only nitration has received much attention. In sulfuric acid at 70°–80°C, 1-nitrobenzo[*c*]cinnoline 6-oxide (43%) and 4-nitrobenzo[*c*]cinnoline 6-oxide (26%) are formed,^{20,120} whereas with nitric acid alone it is reported that the main product is 2-nitrobenzo[*c*]cinnoline-6-oxide (60–70%),^{11,20,120} with some disagreement

¹³³ J. W. Lown and K. Matsumoto, *Can. J. Chem.* **49**, 1165 (1971).

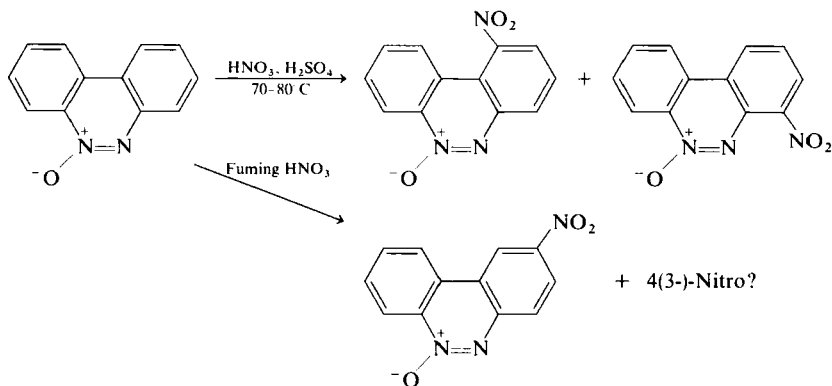
¹³⁴ E. Täuber, *Chem. Ber.* **28**, 451 (1895).

¹³⁵ R. S. W. Braithwaite and P. F. Holt, *J. Chem. Soc.*, 3025 (1959).

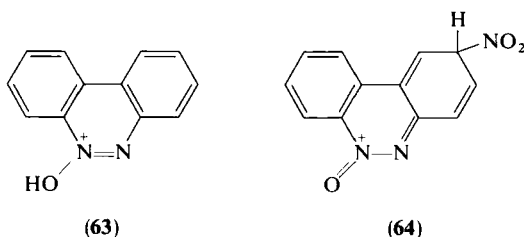
¹³⁶ I. Suzuki, M. Nakadate, and T. Nakashima, *Tetrahedron Lett.*, 2899 (1966).

¹³⁷ S. D. Ross and I. Kuntz, *J. Am. Chem. Soc.* **74**, 1297 (1952).

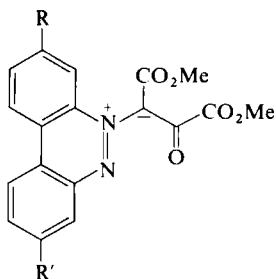
¹³⁸ W. Lüttke, *Z. Electrochem.* **61**, 976 (1957).



SCHEME 5



as to the minor products of the reaction (Scheme 5). It is likely that in the former case nitration takes place via the protonated species **63**, resulting in a substitution pattern like that of benzo[*c*]cinnoline under similar conditions. If, as is more likely in nitric acid alone, nitration takes place via unprotonated *N*-oxide, then the Wheland intermediate leading to 2-substitution would be additionally stabilized by contribution from **64**. Further nitration of 2-nitro-



(65) $\text{R} = \text{R}' = \text{H}$

(66) $\text{R} = \text{OMe}$ $\text{R}' = \text{H}$

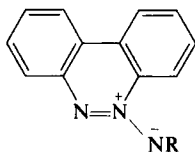
(67) $\text{R} = \text{R}' = \text{OMe}$

benzo[*c*]cinnoline 6-oxide in sulfuric acid takes place at positions 4-, 8-, and 10-.¹³⁹

Recently it has been shown that benzo[*c*]cinnoline 5-oxide, together with its 3-methoxy and 3,8-dimethoxy derivatives, reacts with dimethyl acetylenedicarboxylate under forcing conditions to give low yields of the ylides **65**–**67**, formed by electrocyclic ring opening of the initial 1,3-dipolar cycloadducts.¹⁴⁰ This parallels the process that takes place readily with benzo[*c*]cinnoline *N*-imides (Section IV,F).

F. *N*-AMINATION. BENZO[*c*]CINNOLINE *N*-IMIDES

The reaction of benzo[*c*]cinnoline with aminating agents such as *O*-mesitylsulfonylhydroxylamine gives the dipolar benzo[*c*]cinnoline 5-imide (**23**).⁸⁰ The same compound is formed by thermal rearrangement of



(**23**) R = H

(**68**) R = Me

(**69**) R = CO₂Et

(**70**) R = COMe

(**71**) R = CPh

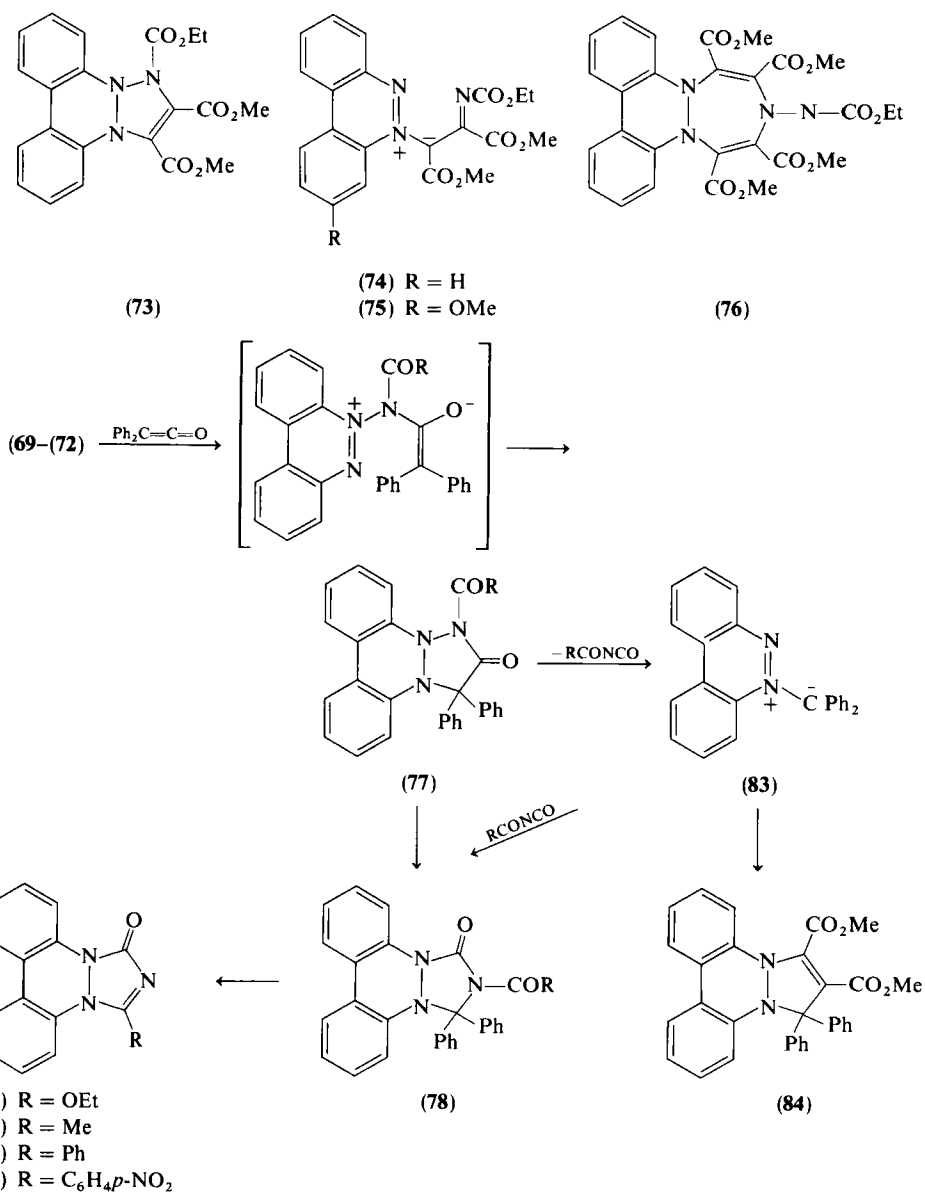
(**72**) R = COC₆H₄*p*-NO₂

dibenzo[*d,f*][1,2,3]triazepine (Section II,E,2).^{79,80} The imide **23** is a stable, yellow crystalline solid, forming a stable hydrochloride. The imide function is, however, easily removed by treatment with nitrous acid or by catalytic hydrogenation. The imide hydrogen is readily replaced by acyl, alkyl, and alkoxy carbonyl groups to give the imides **68**–**72**. Thermal decomposition of **23** in refluxing 1,2-dichlorobenzene gives carbazole in high yield, in contrast to the decomposition of the methyl derivative **68**, where the sole product is benzo[*c*]cinnoline. The *N*-acyl- and *N*-alkoxy carbonyl imides give mixtures of the corresponding *N*-substituted carbazoles with benzo[*c*]cinnoline, formation of *N*-ethoxycarbonylnitrene as a fragment in the thermolysis of **69** being demonstrated by solvent interception. On photolysis the imide **23** and derivatives **68**–**72** are all converted into benzo[*c*]cinnoline.

¹³⁹ M. Ohta, Japanese Patent 75,100,067 (1975) [*CA* **84**, P44108 (1976)].

¹⁴⁰ S. R. Challand, C. W. Rees, and R. C. Storr, *J. Chem. Soc., Chem. Commun.*, 837 (1973).

Imides of this type behave as 1,3-dipolar reagents in cycloaddition reactions.¹⁰¹ For example, imide **69** reacts readily with dimethyl acetylenedicarboxylate to form the cycloadduct **73**, but this undergoes spontaneous

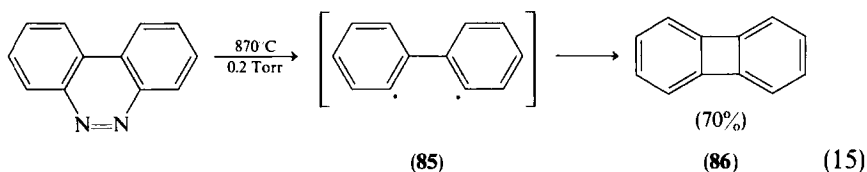


SCHEME 6

electrocyclic ring opening, and the product isolated is the ylide **74**. The regioselectivity of this process is shown by the exclusive conversion of 3-methoxybenzo[*c*]cinnoline-6-ethoxycarbonylimide into ylide **75**. Surprisingly, the ylide **74** behaves as a 1,5- rather than a 1,3-dipolar reagent (see Section IV,A), adding a second molecule of the ester to give the triazepine **76** as primary product.¹⁴¹ Other related cycloadditions with ketenes have been reported recently.^{142,143} The imides **69–72** react with diphenylketene to give the rearranged products **78**, which are hydrolyzed by acid to the triazolinones **79–82** and benzophenone (Scheme 6). Probable intermediates in the formation of products **78** are the cycloadducts **77**, which could rearrange to these directly, or via the ylide **83**. The intermediacy of ylide **83** was indicated by the formation of **84** when the reaction of **71** with diphenylketene was carried out in dimethyl acetylenedicarboxylate.

G. EXTRUSION REACTIONS

The ready loss of nitrogen from the parent ion in the mass spectrum of benzo[*c*]cinnoline (Section III,D) has a parallel in its thermal decomposition; on vacuum pyrolysis at temperatures above 800°C it is converted into biphenylene (**86**) in high yield [Eq. (15)].¹²² The absence of by-products in



the reaction suggests direct formation and ring closure of the diradical intermediate **85**. The scope of the reaction as regards benzo[*c*]cinnoline derivatives is not yet known, although octachlorobenzo[*c*]cinnoline is found to extrude nitrogen at a lower temperature. Preliminary experiments indicate that the effects of substituents show some similarity to those observed in mass spectral fragmentation.¹⁴⁴

¹⁴¹ S. F. Gait, M. J. Rance, R. W. Stephenson, and R. C. Storr, *J.C.S. Perkin I*, 556 (1975).

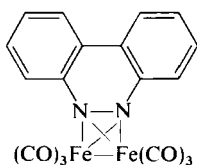
¹⁴² J. J. Barr and R. C. Storr, *J. Chem. Soc., Chem. Commun.*, 788 (1975).

¹⁴³ S. H. Alsop, J. J. Barr, R. C. Storr, A. F. Cameron, and A. A. Freer, *J. Chem. Soc., Chem. Commun.*, 888 (1976).

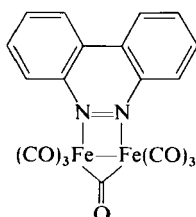
¹⁴⁴ R. B. Walker, Ph.D. Thesis, University of Bristol (1976).

H. METAL-COMPLEX FORMATION

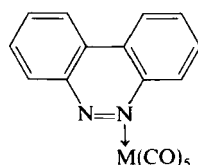
Like other cyclic compounds having a *cis*-azo linkage, benzo[*c*]cinnoline forms fairly stable complexes with many transition metal salts.¹⁴⁵⁻¹⁴⁸ These all have a 1:1 ligand:metal ratio except in the case of palladium(II) chloride, where a 2:1 complex has been isolated.¹⁴⁷ Benzo[*c*]cinnoline 5-oxide also gives 2:1 complexes with palladium(II) chloride and with silver nitrate.¹⁴⁷ A nickel(0) complex, $\text{Ni}(\text{PEt}_3)_2(\text{benzo}[c]\text{cinnoline})_2$, has been obtained by reaction with biscyclooctadiene nickel and triethylphosphine in hexane.¹⁴⁹



(87)



(88)



(89) M = Cr, Mo, W

Benzo[*c*]cinnoline reacts with iron pentacarbonyl in refluxing tetralin to give the red hexacarbonyldi-iron complex **87**.⁹⁸ The reaction with di-iron nonacarbonyl at room temperature gives mainly the blue-black, carbonyl-bridged complex **88**, together with a smaller amount of **87**.¹⁵⁰ Complex **88** loses the carbonyl bridge on heating, forming **87**. Oxidation of complex **87** with ceric ammonium nitrate regenerates benzo[*c*]cinnoline, while reduction with lithium aluminum hydride gives 2,2'-diaminobiphenyl.⁹⁸ Ligand displacement reactions of **87** with phosphines, etc., have been described,^{151,152} and also cycloadditions with alkynes that involve insertion into an N—Fe bond.¹⁵³

The simple carbonyl complexes **89** have recently been prepared indirectly by reactions of benzo[*c*]cinnoline with norbornadiene metal complexes $\text{M}(\text{C}_7\text{H}_8)(\text{CO})_4$.⁹⁷

¹⁴⁵ J. J. Porter and J. L. Murray, *J. Am. Chem. Soc.* **87**, 1628 (1965).

¹⁴⁶ J. R. Allen, G. A. Barnes, and D. H. Brown, *J. Inorg. Nucl. Chem.* **33**, 3765 (1971).

¹⁴⁷ J. J. Porter, J. L. Murray, and K. B. Takvorian, *J. Heterocycl. Chem.* **10**, 43 (1973).

¹⁴⁸ R. Hüttel and A. Konietzny, *Chem. Ber.* **106**, 2098 (1973).

¹⁴⁹ S. D. Ittel and J. A. Ibers, *Inorg. Chem.* **14**, 1183 (1975).

¹⁵⁰ M. Herberhold and K. Leonhard, *J. Organomet. Chem.* **78**, 253 (1974).

¹⁵¹ P. C. Ellgen and S. L. McMullin, *Inorg. Chem.* **12**, 2004 (1973).

¹⁵² P. C. Ellgen and J. N. Gerlach, *Inorg. Chem.* **13**, 1944 (1974).

¹⁵³ A. Albini and H. Kisch, *J. Organomet. Chem.* **101**, 231 (1975).

V. Physical and Chemical Properties of Substituted Benzo[*c*]cinnolines

A. ALKYL AND ARYL DERIVATIVES

The four monomethylbenzo[*c*]cinnolines have been prepared by the photocyclization of azobenzenes,⁶⁰ also the 1,8-, 1,10-, 2,4-, 2,9-, 3,8-, and 4,7-dimethyl,^{60,65} the 1,2,4-trimethyl,⁶⁵ and the 1-, 2-, and 3-phenyl^{61,62} derivatives. Several of these have also been made by cyclization of biaryls,^{13,15,23,108,118,154} as have 2,3,8,9-tetramethyl and 2,3,4,7,8,9-hexamethylbenzo[*c*]cinnolines.¹⁵⁵ Like the corresponding phenanthrene derivatives, benzo[*c*]cinnolines having bulky groups at positions 1 and 10 should be nonplanar and optically resolvable. An unsuccessful attempt to resolve 1,10-dimethylbenzo[*c*]cinnoline has been reported.²³ The corresponding 4,7-diamino compound has been resolved but racemizes easily.¹²¹

Apart from some nitration studies (Section IV,B), the only reaction of these derivatives to be described has been the side-chain oxidation of 2,9-dimethylbenzo[*c*]cinnoline to 2-methylbenzo[*c*]cinnoline-9-carboxylic acid using chromic acid.¹⁵⁴

B. CARBONYL-CONTAINING DERIVATIVES AND NITRILES

Benzo[*c*]cinnoline aldehydes are as yet unknown. The 2- and 3-acetyl derivatives have been prepared,⁶³ but the majority of known compounds relevant to this section are mono- and dicarboxylic acid derivatives. These include the 2-,^{65,75,102,156} 3-,^{65,102} and 4-^{65,102,155,157} monoacids and esters, the lactone of 10-hydroxybenzo[*c*]cinnoline-1-carboxylic acid,⁶⁵ some halogeno- and methyl-substituted 2-¹⁵³ and 4-^{67,157} carboxylic acids, and the 2,9-,^{66,158,159} 3,8-,^{15,66,160} and 4,7-⁶⁶ dicarboxylic acids and derivatives. These compounds have been obtained by ring synthesis, or, in the case of 2-methylbenzo[*c*]cinnoline-9-carboxylic acid, by side-chain oxidation,¹⁵⁴ rather than by the introduction of substituents into benzo[*c*]cinnoline. Benzo[*c*]cinnoline-1-carbonitrile has been prepared, albeit in low

¹⁵⁴ L. Meyer, *Chem. Ber.* **26**, 2238 (1893).

¹⁵⁵ I. Puskas, E. K. Fields, and E. M. Banas, *Am. Chem. Soc., Div. Pet. Chem., Prepr.* **17**, B6 (1972).

¹⁵⁶ G. E. Lewis and J. A. Reiss, *Aust. J. Chem.* **21**, 1097 (1968).

¹⁵⁷ C. P. Joshua and G. E. Lewis, *Aust. J. Chem.* **20**, 929 (1967).

¹⁵⁸ F. A. Neugebauer, *Tetrahedron* **26**, 4843 (1970).

¹⁵⁹ M. Reiger and F. H. Westheimer, *J. Am. Chem. Soc.* **72**, 28 (1950).

¹⁶⁰ E. Honold, German Patent 555,182 (1931) [*CA* **26**, 5214 (1932)].

yield, by a Sandmeyer reaction of 1-aminobenzo[c]cinnoline¹⁶¹; the 2,9-dinitrile is also known.¹⁵⁸

Apart from esterification reactions and thermal decarboxylation of the 2-carboxylic acid, the only other reaction to be reported is the Beckmann rearrangement of the oxime of 3-acetylbenzo[c]cinnoline, which proceeds normally to give the 3-amino compound.⁶³

C. NITROGEN-CONTAINING DERIVATIVES

Nitration of benzo[c]cinnoline (Section IV,B) gives the 1-nitro, 4-nitro, and 1,10-dinitro derivatives,^{20,118-120} the first being the most readily available. Others, such as 2- and 3-nitrobenzo[c]cinnolines, are obtainable by nonreductive ring synthesis methods.^{20,63,94,118} The 2-phenylazo compound has also been described.⁶²

Chemical or catalytic reduction of the mononitro^{20,118-120} and 1,10-dinitro¹⁶² derivatives give the corresponding amines. The 2-amino compound is more easily obtainable by reduction of 2-nitrobenzo[c]cinnoline 6-oxide^{11,20} or by the photocyclization of 4-benzalaminoazobenzene,⁶³ while the least accessible 3-isomer has been prepared by reductive cyclization of 2,2',4-trinitrobiphenyl,^{10,20} as has the 3,8-diamine from 2,2'-dinitrobenzidine.⁹ The 2-, 3-, and 4-amino-compounds have also been obtained from reactions of halogenobenzo[c]cinnolines with potassium amide¹⁶³ (Section V,E). Dialkylamino derivatives have been prepared by heating the corresponding chlorobenzo[c]cinnoline with a dialkylamine under pressure.⁶⁴

The monoaminobenzo[c]cinnolines form intensely colored solutions in mineral acids (for discussion, see Lewis and Reiss⁶⁴). In their reactions, acylation, diazotization, etc., they behave as typical aromatic amines.

D. OXYGEN-CONTAINING DERIVATIVES

Methoxybenzo[c]cinnolines have been prepared by cyclization of methoxylated precursors,^{5,6,15,80,164} and, in the case of the 2- and 4-isomers, by the action of sodium methoxide on the monochloro compounds.¹⁵⁶ They are demethylated to the hydroxy derivatives by heating with hydrobromic

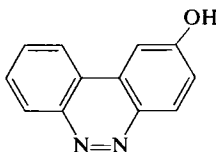
¹⁶¹ M. A. Cockett, B.Sc. Thesis, University of Bristol (1960).

¹⁶² P. F. Holt and A. N. Hughes, *J. Chem. Soc.*, 3216 (1960).

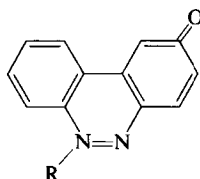
¹⁶³ G. E. Lewis, R. H. Prager, and R. H. M. Ross, *Aust. J. Chem.* **28**, 2057 (1975).

¹⁶⁴ K. Hata, K. Tatematsu, and B. Kubota, *Bull. Chem. Soc. Jpn.* **10**, 425 (1935).

acid⁵ or with aluminum chloride¹⁶⁵ in the usual way. Reduction of 2,2'-dinitrobiphenyl-4-sulfonic acid gives benzo[*c*]cinnoline-3-sulfonic acid, which is converted into 3-hydroxybenzo[*c*]cinnoline by alkali fusion¹⁶⁶; the 3,8-dihydroxy-compound is obtained by a similar method. The 3-hydroxy compound and its 6-oxide are also formed by the base-catalyzed rearrangement of 3'-hydroxy-2-nitrobenzenesulfonanilide^{37,80} (Section II,A,2).



(90)



(91) R = H

(92) R = Me

Of the four monohydroxybenzo[*c*]cinnolines the 2- and the 4-isomers are potentially tautomeric with the corresponding quinonimines, e.g., **90** \rightleftharpoons **91**. While the ultraviolet spectrum of 2-hydroxybenzo[*c*]cinnoline shows close correspondence to that of the 2-methoxy compound in neutral solution, spectra of the conjugate acid and conjugate base both indicate appreciable charge-resonance between the 2- and 6-positions, and methylation of **90** with dimethyl sulfate or diazomethane gives rise to mixtures of 2-methoxybenzo[*c*]cinnoline and the quinonimine **92**.^{5,165}

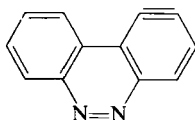
E. HALOGEN DERIVATIVES

Of the halogenobenzo[*c*]cinnolines the 1-bromo, 4-bromo, and 1,4-dibromo are obtainable by direct bromination^{95,100} (Section IV,B). Some, including the 2- and 3-monobromo compounds, have been prepared by the cyclization of halogenobiphenyls,^{13,20,38,94} and others, including all the monochloro and moniodo isomers, by the photocyclization of halogenoazobenzenes.^{65,68} Several have also been prepared by Sandmeyer reactions of aminobenzo[*c*]cinnolines.^{14,20,95}

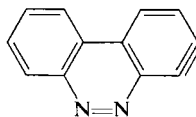
Nucleophilic displacements of halogen occur with alkoxides, dialkylamines and their salts, and potassium amide. Thus, all of the dimethylamino compounds have been prepared by heating the monochlorobenzo[*c*]cinnolines with dimethylamine under pressure⁶⁴; apparently the sterically hindered 1-chloro isomer is less reactive than the others under these conditions.

¹⁶⁵ G. E. Lewis, D. L. Lill, R. H. Prager, and J. A. Reiss, *Aust. J. Chem.* **23**, 619 (1970).

¹⁶⁶ O. Goll, German Patent 577,631 (1933) [*CA* **28**, 654 (1934)].



(93)



(94)

Reactions of the chloro compounds with lithium dimethylamide are complicated by the fact that nucleophilic displacement of hydrogen often precedes that of chlorine, giving complex mixtures of products.^{68,123} The results obtained in reactions of potassium amide with chloro- and iodobenzo[*c*]cinnolines show that elimination-addition processes via arynes **93** and **94** are more important than direct nucleophilic displacement (addition-elimination).¹⁶³ Surprisingly, no 1-aminobenzo[*c*]cinnoline is formed from the 1- and 2-halogeno compounds, while 4-chlorobenzo[*c*]cinnoline gives small amounts of 2-aminobenzo[*c*]cinnoline by a 1,3-displacement.

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Developments in the Chemistry of Reissert Compounds (1968–1978)

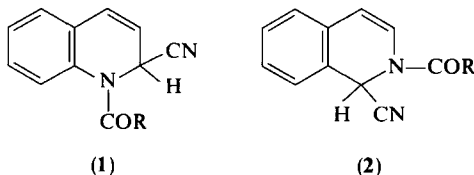
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I. Introduction

The chemistry of Reissert compounds, for example, *N*-acyldihydroquin-aldonitriles (**1**) and *N*-acyldihydroisoquinaldonitriles (**2**), was the subject of a review in an earlier volume of this series.¹ The application of Reissert compounds to the synthesis of isoquinoline alkaloids and related compounds



¹ F. D. Popp, *Adv. Heterocycl. Chem.* **9**, 1 (1968).

has also been reviewed.² The present review covers the developments in the chemistry of Reissert compounds from the last review in this series¹ to late 1978 and will follow, as far as possible, the same general format as the previous review.

Detailed procedures for the synthesis and some reactions of Reissert compounds have appeared in compendia of synthetic procedures.^{3,4}

II. Preparation

A. METHODS

A few new Reissert compounds have been made by the aqueous method,^{1,5-10} but the vast majority by the methylene chloride-water solvent system.¹ A new variation of the latter method, which is particularly useful in cases where pseudo-base formation becomes a problem,^{11,12} adds a small quantity of benzyltrialkylammonium chloride to the reaction mixture.¹¹⁻¹³ The phase transfer agent appears to enhance the transport of the cyanide ion to the methylene chloride phase.

Two new methods of Reissert compound formation have appeared. Silver cyanide and benzoyl chloride in chloroform is effective¹⁴ in the 1,6-naphthyridine series. Reissert compounds have been prepared from quinoline or isoquinoline and an acid chloride, using trimethylsilyl cyanide and a catalytic amount of aluminum chloride in methylene chloride.^{15,15a} The Reissert compound of 6,7-dimethoxyphthalazine has also been prepared using this latter method.^{15b}

² F. D. Popp, *Heterocycles* **1**, 165 (1973).

³ F. D. Popp, *Synth. Proc. Heterocycl. Chem.* **1**, in press (1979).

⁴ B. C. Uff, J. R. Kershaw, and J. L. Neumeyer, *Org. Synth.* **56**, 19 (1977).

⁵ J. C. Belsten and S. F. Dyke, *J. Chem. Soc. C*, 2073 (1968).

⁶ R. M. Coomes, J. R. Falck, D. K. Williams, and F. R. Stermitz, *J. Org. Chem.* **38**, 3701 (1973).

⁷ Y. Hamada, I. Takeuchi, and H. Matsuoka, *Chem. Pharm. Bull.* **18**, 1026 (1970).

⁸ F. R. Stermitz and D. K. Williams, *J. Org. Chem.* **38**, 1761 (1973).

⁹ T. Sugawara, T. Toyota, K. Sasakura, and T. Hidaka, *Chem. Pharm. Bull.* **19**, 1971 (1971).

¹⁰ I. Takeichi and Y. Hamada, *Chem. Pharm. Bull.* **24**, 1813 (1976).

¹¹ D. Bhattacharjee and F. D. Popp, *Heterocycles* **6**, 1905 (1977).

¹² B. C. Uff and R. D. Budram, *Heterocycles* **6**, 1789 (1977).

¹³ T. Koizumi, K. Takeda, K. Yoshida, and E. Yoshii, *Synthesis*, 497 (1977).

¹⁴ Y. Kobayashi, I. Kumadaki, and H. Sato, *Chem. Pharm. Bull.* **17**, 2614 (1969).

¹⁵ S. Ruchirawat, N. Phadungkul, M. Chuankamnerdkarn, and C. Thebtaranonth, *Heterocycles* **6**, 43 (1977).

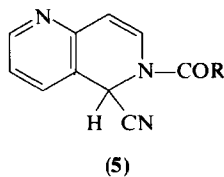
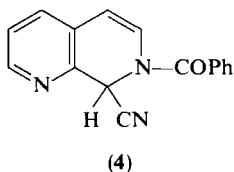
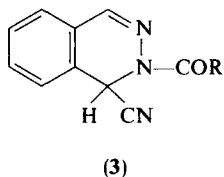
^{15a} S. Ruchirawat, S. Suparlucknaree, and N. Prasitpan, *Heterocycles* **9**, 859 (1978).

^{15b} D. Bhattacharjee and F. D. Popp, Unpublished results, 1978.

B. Heterocyclic Bases

Most work has been in the isoquinoline area, principally because of the usefulness of isoquinoline Reissert compounds in the synthesis of isoquinoline alkaloids.² Aside from 5-chloro-⁷ and 3-acetylaminomethylquinoline⁹ and a few halo,^{5,16-18} methyl,^{16,19} and carbomethoxyisoquinolines,²⁰ all the substituted quinoline or isoquinoline Reissert compounds have involved oxygen-type functions in one or more of positions 4-, 5-, 6-, 7-, and 8- of the isoquinoline ring.^{6,8,15,20-38}

In the area of diazaheterocyclic compounds, additional work has been reported on compounds **3** from phthalazine.^{11,12,15b,29,39,40} A Reissert compound (**4**) has been obtained from 1,7-naphthyridine,¹⁰ and several (**5**) have



¹⁶ S. R. Chhabra, J. R. Kershaw, and B. C. Uff, *Tetrahedron Lett.*, 3199 (1967).

¹⁷ G. W. Kirby, S. L. Tan, and B. C. Uff, *Chem. Commun.*, 1075 (1969).

¹⁸ H. Reimlinger, J. J. M. Vandewalle, W. R. F. Lingier, and E. DeRuiter, *Chem. Ber.* **108**, 3771 (1975).

¹⁹ H. W. Gibson, *J. Heterocycl. Chem.* **7**, 1169 (1970).

²⁰ S. F. Dyke, A. W. C. White, and D. Hartley, *Tetrahedron* **29**, 857 (1973).

²¹ D. P. Aysola and M. S. Gibson, *Can. J. Chem.* **55**, 435 (1977).

²² M. P. Cava and I. Noguchi, *J. Org. Chem.* **37**, 2936 (1972).

²³ A. J. Birch, A. H. Jackson, and P. V. R. Shannon, *Tetrahedron Lett.*, 4789 (1972).

²⁴ A. J. Birch, A. H. Jackson, and P. V. R. Shannon, *J.C.S. Perkin I*, 2190 (1974).

²⁵ M. P. Cava and M. Srinivasan, *Tetrahedron* **26**, 4649 (1970).

²⁶ S. F. Dyke and A. C. Ellis, *Tetrahedron* **28**, 3999 (1972).

²⁷ M. P. Cava, M. V. Lakshmikantham, and M. J. Mitchell, *J. Org. Chem.* **34**, 2665 (1969).

²⁸ M. P. Cava and I. Noguchi, *J. Org. Chem.* **38**, 61 (1973).

²⁹ M. J. Cook, A. R. Katritzky, and A. D. Page, *J. Am. Chem. Soc.* **99**, 165 (1977).

³⁰ H. W. Gibson, D. K. Chesney, and F. D. Popp, *J. Heterocycl. Chem.* **9**, 541 (1972).

³¹ A. H. Jackson and G. W. Stewart, *Chem. Commun.*, 149 (1971).

³² A. H. Jackson, G. W. Stewart, G. A. Charnock, and J. A. Martin, *J.C.S. Perkin I*, 1911 (1974).

³³ A. H. Jackson and G. W. Stewart, *Tetrahedron Lett.*, 4941 (1971).

³⁴ J. Knabe and A. Frie, *Arch. Pharm. (Weinheim)* **306**, 648 (1973).

³⁵ B. C. Uff and J. R. Kershaw, *J. Chem. Soc. C*, 666 (1969).

³⁶ B. C. Uff, J. R. Kershaw, and S. R. Chhabra, *J.C.S. Perkin I*, 479 (1972).

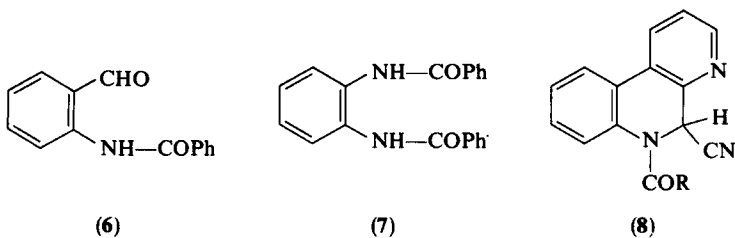
³⁷ B. C. Uff, J. R. Kershaw, and S. R. Chhabra, *J.C.S. Perkin I*, 1146 (1974).

³⁸ F. D. Popp, R. E. Buhts, and D. K. Chesney, *J. Heterocycl. Chem.* **15**, 429 (1978).

³⁹ F. D. Popp, J. M. Wefer, and C. W. Klinowski, *J. Heterocycl. Chem.* **5**, 879 (1968).

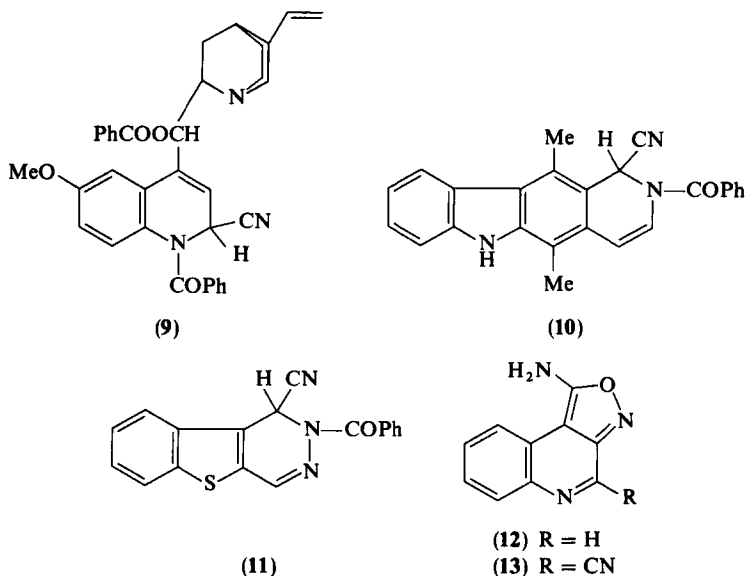
⁴⁰ F. D. Popp, D. Bhattacharjee, and H. Heller, unpublished work (1975-1977).

been reported from 1,6-naphthyridine.^{7,14} Both quinazoline³⁷ and quinoxaline⁴¹ on attempted Reissert compound formation undergo ring opening, to give **6** and **7**, respectively. Reissert compounds **8** have been reported.⁴²



Reissert compounds **9** and **10** have been obtained from the alkaloids quinine and ellipticine.⁴³ Compound **11**, which can be considered as related to the phthalazine Reissert compounds, has been obtained from the corresponding benzothienopyridazine.⁴⁴

Treatment of **12** with benzoyl chloride and potassium cyanide, followed by chromatography on alumina, gave **13**,⁴⁵ evidently via a Reissert derivative.



⁴¹ F. D. Popp and J. M. Wefer, unpublished work (1966).

⁴² Y. Hamada, K. Morishita, and M. Hirota, *Chem. Pharm. Bull.* **26**, 350 (1978).

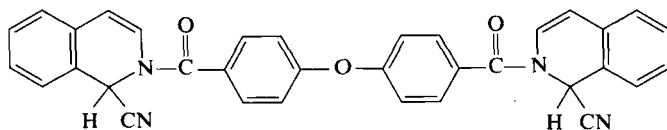
⁴³ F. D. Popp, unpublished work (1976–1978).

⁴⁴ G. Dore, M. Bonhomme, and M. Robba, *Tetrahedron* **28**, 2553 (1972).

⁴⁵ T. Okamoto and H. Takahashi, *Chem. Pharm. Bull.* **19**, 1809 (1971).

C. ACID HALIDES

In addition to benzoyl chloride, a number of mono- and disubstituted benzoyl halides have been used^{16,18,19,21,29,36,38,46,47} in Reissert compound formation, as have acyl halides of furan³⁴ and thiophene-1-carboxylic acids.^{34,48} Besides simple aliphatic carboxylic acid halides, some ω -haloacyl halides^{30,48,49} and pentafluorophenylacetyl chloride⁴⁸ have been used. 4,4'-Oxydibenzoyl chloride with isoquinoline gave the Reissert compound **14**.³⁸



(14)

III. Chemical Properties and Reactions

A. REACTIONS UNDER ACIDIC CONDITIONS

Except for a demonstration that the phthalazine Reissert compound (3: R = Ph) behaves normally in giving benzaldehyde on acid-catalyzed hydrolysis,³⁹ no new reports have appeared of Reissert compounds being used in aldehyde synthesis. Acid-catalyzed hydrolysis has been used, however, in some cases to prepare heterocyclic carboxylic acids. Thus in addition to the preparation of isoquinaldic acid,⁵⁰ phthalazine-1-carboxylic acid³⁹ and **15**⁴⁴ have been prepared from 3(R = Ph) and **11**, respectively. Acid-catalyzed hydrolysis of **16** occurs with cyclization to give **17**.⁹ A series of Reissert compounds derived from substituted 3-aminoquinolines have been converted to the corresponding quinaldic acids by acid-catalyzed hydrolysis.⁵¹

The cation isolated from treatment of Reissert compounds with acid has generally been written as **18**.^{1,52} A detailed study²⁹ using a combination

⁴⁶ H. W. Gibson, *Tetrahedron Lett.*, 5549 (1968).

⁴⁷ M. Sainsbury, D. W. Brown, S. F. Dyke, and G. Hardy, *Tetrahedron* **25**, 1881 (1969).

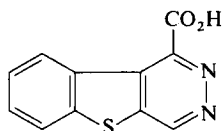
⁴⁸ F. D. Popp, C. W. Klinowski, R. Piccirilli, D. H. Purcell, and R. F. Watts, *J. Heterocycl. Chem.* **8**, 313 (1971).

⁴⁹ F. D. Popp and D. H. Purcell, *Synthesis*, 591 (1970).

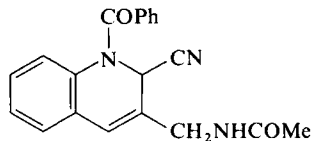
⁵⁰ W. Wiegrebé and D. Sasse, *Arch. Pharm. (Weinheim)* **303**, 145 (1970).

⁵¹ C. K. Chu and T. J. Bardoes, *J. Heterocycl. Chem.* **14**, 1053 (1977).

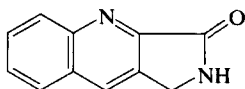
⁵² W. E. McEwen, M. A. Calabro, I. C. Mineo, and I. C. Wang, *J. Am. Chem. Soc.* **95**, 2392 (1973).



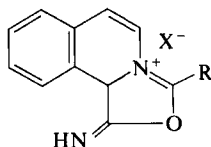
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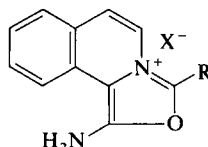
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(18)

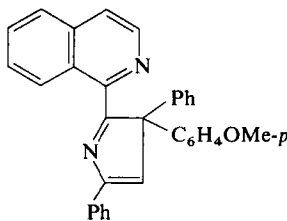


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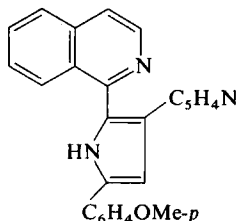
of nuclear magnetic resonance (NMR), deuterium exchange, and mass spectrometry techniques of three isoquinoline Reissert compounds, two phthalazine Reissert compounds, and two dihydro Reissert compounds indicates that Reissert salts do not exist as **18** but that the predominant tautomer is that of the 5-aminooxazolium cation **19**. This structural reassignment does not require any radical reinterpretation of the chemistry of these salts.

Several stable Reissert salts (**19**: X = ClO₄) have been reported,^{34,47,52-54} and reactions with alkynes and alkenes have been studied.

The sulfuric acid-catalyzed condensation of the isoquinoline Reissert compound **2** (R = Ph) with 1-*p*-anisyl-1-phenylethylene proceeds as described for the condensation with 1,1-diphenylethylene to give **20**.⁵⁵ The hydrochloric acid-catalyzed condensation of **2** (R = C₆H₄OMe-*p*) with 2- and 4-vinylpyridine gave **21**: C₅H₄N = 2- and 4-pyridyl, respectively).⁵⁶



(20)



(21)

The reaction of **19** (R = Ph) with ethyl phenylpropiolate gave **23** (R = Et; R = Ph), via the bridged intermediate **22**.⁵³ Use of dimethyl acetylene

⁵³ W. E. McEwen, I. C. Mineo, and Y. H. Shen, *J. Am. Chem. Soc.* **93**, 4479 (1973).

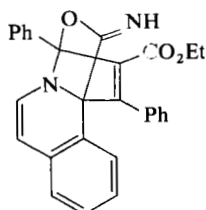
⁵⁴ W. E. McEwen, K. B. Kanitkar, and W. M. Hung, *J. Am. Chem. Soc.* **93**, 4484 (1971).

⁵⁵ W. E. McEwen, D. H. Bertebile, T. K. Liao, and Y. S. Lin, *J. Org. Chem.* **36**, 1459 (1971).

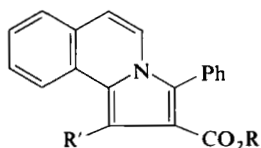
⁵⁶ V. Giridhar and W. E. McEwen, *J. Heterocycl. Chem.* **8**, 121 (1971).

dicarboxylate gave **23** ($R = \text{Me}$; $R' = \text{CO}_2\text{Me}$), and ethyl tetrolate gave **23** [$R = \text{H}$ (hydrolysis), $R' = \text{Me}$]; the use of the quinoline Reissert compound in this sequence was less satisfactory.⁵³ The mechanism of the formation of bridged intermediates of type **22** has been studied,⁵⁴ and it appears to involve a concerted 1,3-dipolar cycloaddition with synchronous formation of two new covalent bonds.

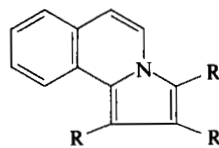
In summary, it appears that Reissert salts undergo 1,3-dipolar addition reactions with reactive acetylenic 1,3-dipolarophiles^{57,58} to give compounds of type **24** and undergo complex condensation-rearrangement reactions with olefinic dienophiles⁵⁷⁻⁵⁹ to give products of the type **25**.



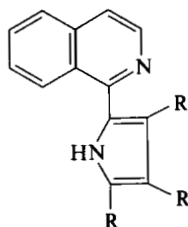
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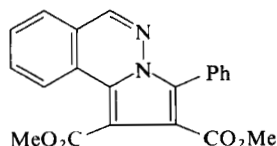
(23)



(24)



(25)



(25a)

Reaction of the fluoroborate salt of **3** ($R = \text{Ph}$) with dimethyl acetylene dicarboxylate gave the pyrrolo[2,1-*a*]phthalazine (**25a**).^{15b}

B. REACTIONS INVOLVING THE FORMATION OF AN ANION OF THE REISSERT COMPOUND

The anion (**26**) derived from the isoquinoline Reissert compound (**2**) and the related anions derived from other Reissert compounds have most generally been generated by the use of sodium hydride in dimethylformamide.¹

⁵⁷ W. E. McEwen, P. E. Stott, and C. M. Zepp, *J. Am. Chem. Soc.* **95**, 8452 (1973).

⁵⁸ W. E. McEwen, C. C. Cabello, M. A. Calabro, A. M. Ortega, P. E. Stott, A. J. Zapata, C. M. Zepp, and J. J. Lubinkowski, *J. Org. Chem.* **44**, 111 (1979).

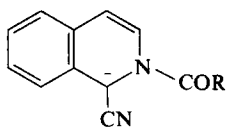
⁵⁹ C. F. Ling, R. P. Santella, Y. H. Shen, and W. E. McEwen, *J. Org. Chem.* **40**, 661 (1975).

The major use of these anions has been in the synthesis of 1-substituted isoquinolines.

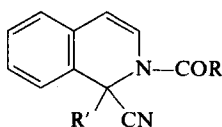
1. Reaction with Alkyl Halides

Phenyllithium,^{5,60} and 50% sodium hydroxide with a catalytic amount of TEBA chloride,⁶¹ or cetrimonium bromide^{61a} have been used in a few instances, instead of sodium hydride, to generate the anion in alkylation reactions. A study^{61a} comparing the use of lithium diisopropylamide in tetrahydrofuran/hexamethylphosphoramide, potassium hydroxide with benzene and dicyclohexyl-18-crown-6, and 50% sodium hydroxide with benzene or acetonitrile and cetrimonium bromide for alkylation concludes that the phase transfer procedure is advantageous. Triton B has sometimes been used as an alternative to aqueous hydroxide for the hydrolysis of **27** to **28**,⁶²⁻⁶⁶ particularly in cases where R = 2-nitrobenzyl.^{22,25,28,67-71}

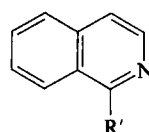
The major application of the alkylation of Reissert compounds (**2**) via **26** to **27** and then hydrolysis to **28** has been in the field of alkaloid synthesis.² Thus, the Reissert alkylation scheme has been used in the synthesis of amurensine and isoamurensine,²⁶ caseadine methyl ether,²⁷ cularine,^{31,32}



(26)



(27)



(28)

⁶⁰ Y. Iizuka, T. Aoki, and T. Sukamoto, Japanese Patent 7596,599 (1975) [*CA* **84**, 30927 (1976)].

⁶¹ M. Makosza, *Tetrahedron Lett.*, 677 (1969).

^{61a} J. W. Skiles and M. P. Cava, *Heterocycles* **9**, 653 (1978).

⁶² J. Knabe and A. Ecker, *Arch. Pharm. (Weinheim)* **307**, 727 (1974).

⁶³ J. Knabe and A. Frie, *Arch. Pharm. (Weinheim)* **306**, 592 (1973).

⁶⁴ J. Knabe and G. Link, *Arch. Pharm. (Weinheim)* **308**, 519 (1975).

⁶⁵ J. Knabe and G. Link, *Arch. Pharm. (Weinheim)* **308**, 151 (1975).

⁶⁶ J. Knabe and G. Link, *Arch. Pharm. (Weinheim)* **309**, 72 (1976).

⁶⁷ M. P. Cava and M. V. Lakshmikantham, *J. Org. Chem.* **35**, 1867 (1970).

⁶⁸ D. R. Elmaleh, F. E. Granchelli, and J. L. Neumeyer, *J. Heterocycl. Chem.* **16**, 87 (1979).

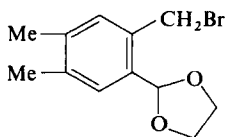
⁶⁹ J. L. Neumeyer, F. E. Granchelli, K. Fuxe, U. Ungerstedt, and H. Corrodi, *J. Med. Chem.* **17**, 1090 (1974).

⁷⁰ W. S. Saari, U.S. Patent 3,810,987 (1974).

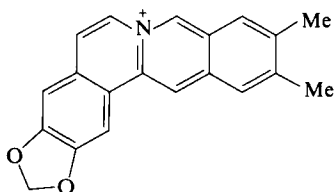
⁷¹ W. S. Saari, S. W. King, V. J. Lotti, and A. Scriabine, *J. Med. Chem.* **17**, 1086 (1974).

2,3-demethoxycoralayne,⁷² 2,9-dimethoxy-3-hydroxypavinane,⁶ eschola-
mine,^{23,24} munitagine,⁷³ petaline,³⁶ platycerine,⁸ takatonine,^{23,24} and a
variety of oxygenated benzyloquinolines.^{20,33,38,74-79}

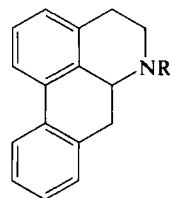
An interesting sequence involved the alkylation of the Reissert compound
derived from 6,7-methylenedioxyisoquinoline with **29** to give **30** after several
steps.⁶⁰



(29)



(30)



(31)

The use of 2-nitrobenzyl halides in the Reissert alkylation, followed even-
tually by the Pschorr cyclization, has provided an attractive route to various
aporphines (**31**). Thus this procedure had led to the synthesis of apomor-
phine,^{80,81} apomorphine derivatives,⁸² atheroline,²² imenine,²⁸ *N*-methyl-
ovigerine,²⁵ oconovine,⁶⁷ 8-hydroxyaporphines,⁸³ 10-hydroxyaporphines,⁸⁴
11-hydroxyaporphines,⁶⁹⁻⁷¹ 9,10-dihydroxyaporphines,⁸⁵ and other apor-

⁷² K. Y. Zee-Cheng, K. D. Paull, and C. C. Cheng, *J. Med. Chem.* **17**, 347 (1974).

⁷³ F. R. Stermitz, D. K. Williams, S. Natarajan, M. S. Premila, and B. R. Pai, *Indian J. Chem.* **12**, 1249 (1974).

⁷⁴ A. J. Birch, A. H. Jackson, P. V. R. Shannon, and G. W. Stewart, *J.C.S. Perkin I*, 2492 (1975).

⁷⁵ M. Ikezaki, K. Irie, N. Umino, K. Ikezawa, and M. Satoh, Japanese Patent 76 70,771 (1976) [*CA* **86**, 106408 (1977)].

⁷⁶ M. Ikezaki, K. Irie, N. Umino, K. Ikezawa, and M. Satoh, Japanese Patent 76 70,772 (1976) [*CA* **86**, 72465 (1977)].

⁷⁷ M. Ikezaki, K. Irie, N. Umino, K. Ikezawa, and M. Satoh, Japanese Patent 76 70,774 (1976) [*CA* **86**, 106409 (1977)].

⁷⁸ K. A. Jaeggi, K. Kocsis, and U. Renner, German Patent 2,026,486 (1970) [*CA* **74**, 53568 (1971)].

⁷⁹ J. Sam and A. J. Bej, *J. Pharm. Sci.* **56**, 1441 (1967).

⁸⁰ J. L. Neumeyer, B. R. Neustadt, K. H. Oh, K. K. Weinhardt, C. B. Boyce, F. J. Rosenberg, and D. G. Teiger, *J. Med. Chem.* **16**, 1223 (1973).

⁸¹ J. L. Neumeyer, B. R. Neustadt, and J. W. Weintraub, *J. Pharm. Sci.* **59**, 1850 (1970).

⁸² J. L. Neumeyer, U.S. Patent 3,717,639 (1973).

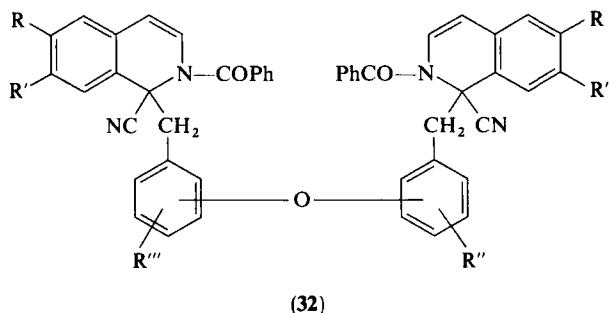
⁸³ J. L. Neumeyer, W. P. Däfeldecker, B. Costall, and R. J. Naylor, *J. Med. Chem.* **20**, 190 (1977).

⁸⁴ J. L. Neumeyer, J. F. Reinhard, W. P. Däfeldecker, J. Guarino, D. S. Kosersky, K. Fuxe, and L. Agnati, *J. Med. Chem.* **19**, 25 (1976).

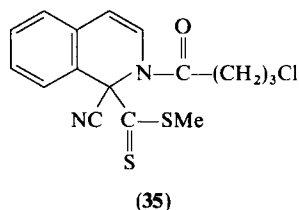
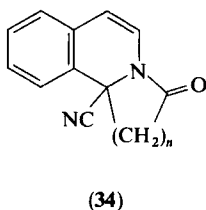
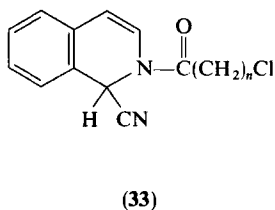
⁸⁵ J. L. Neumeyer, M. McCarthy, S. P. Battista, F. J. Rosenberg, and D. G. Teiger, *J. Med. Chem.* **16**, 1228 (1973).

phine derivatives.^{68,86,87} 2-Iodobenzyl halides have been also used in Reissert alkylation sequences to lead eventually to aporphines through photocyclizations⁸⁶ and electrochemical cyclizations.⁸⁸ Nitrobenzylisoquinolines have been prepared for mass spectral studies via this synthetic route.⁸⁹

A number of dihalides have been used to alkylate 2 mol of the Reissert compound.^{48,90,91} This procedure has been applied to the synthesis of various bisbenzylisoquinolines through formation of **32**.⁹¹



Reissert compounds of the type **33** ($n = 3$ ^{30,49} and 4 ³⁰) undergo an intramolecular alkylation on treatment with sodium hydride in dimethylformamide to give the tricyclic compounds (**34**). A similar reaction also takes place in the quinoline series.³⁰ When **33** ($n = 3$) and isopropyl bromide are treated with sodium hydride, cyclization to **34** ($n = 3$) takes place rather than alkylation with the isopropyl bromide; however, treatment of **33** ($n = 3$) and carbon disulfide-methyl iodide with sodium hydride gives **35** rather than cyclization.³⁰ Alkaline peroxide converts the nitrile **34** ($n = 3$) into an amide, and acid or base hydrolysis gives 4-(1-isoquinoly)butyric acid.³⁰



⁸⁶ J. L. Neumeyer, K. H. Oh, K. K. Weinhardt, and B. R. Neustadt, *J. Org. Chem.* **34**, 3786 (1969).

⁸⁷ J. L. Neumeyer, C. Perianayagam, S. Ruchirawat, H. S. Feldman, B. H. Takman, and P. A. Tenthorpe, *J. Med. Chem.* **20**, 894 (1977).

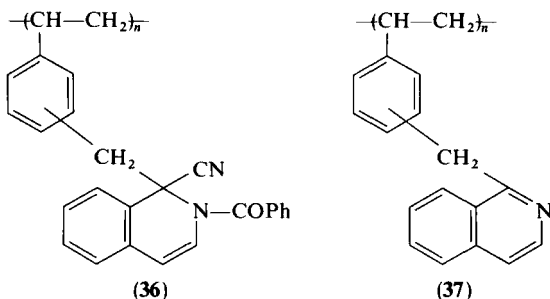
⁸⁸ R. Gottlieb and J. L. Neumeyer, *J. Am. Chem. Soc.* **98**, 7108 (1976).

⁸⁹ P. Vouros, B. Petersen, W. P. Däfeldecker, and J. L. Neumeyer, *J. Org. Chem.* **42**, 744 (1977).

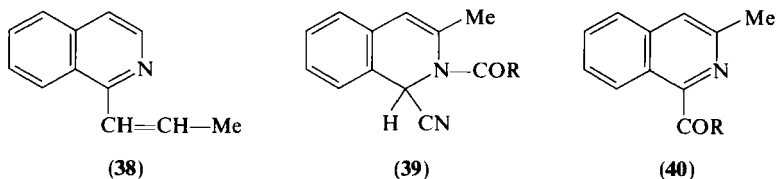
⁹⁰ R. M. Piccirilli, E. O. Snoke, R. F. Watts, and F. D. Popp, *J. Pharm. Sci.* **67**, 740 (1978).

⁹¹ D. C. Smith and F. D. Popp, *J. Heterocycl. Chem.* **13**, 573 (1976).

A number of polymers containing a heterocyclic group have been prepared using the Reissert alkylation sequence.⁹²⁻⁹⁴ Thus, for example, the reaction of the isoquinoline Reissert anion (**26**) with poly(vinylbenzyl chloride) and sodium hydride gave **36**, which on hydrolysis with base gave **37**.^{92,93} A similar condensation takes place with quinoline, phenanthridine, and benzo-[*f*]quinoline Reissert compounds.⁹⁴ The Reissert anion **26** has also been alkylated with a mixture of *m*- and *p*-vinylbenzyl chloride and the product polymerized to a polymer of type **37**.⁹³ Copolymerization has also been studied.⁹³



The anion of the isoquinoline Reissert compound (**26**) has also been alkylated with a wide variety of other alkyl halides.^{5,19,35,38,48,62-66,90,93} The alkylation product from **26** and allyl chloride undergoes isomerization to **38** on base-catalyzed hydrolysis.⁹⁰ The phthalazine Reissert compound (**3**) has also been alkylated, in the presence of sodium hydride, with methyl iodide³⁹ and with benzyl halides⁴⁰ to give, after hydrolysis, 1-substituted phthalazines. A phthalazine analog of **34** ($n = 3$) has been prepared.^{15b} An additional example of the alkylation of the quinoline Reissert compound in the 4-position has appeared.^{94a}



Alkylation of the Reissert compound of 3-methylisoquinoline is not as straightforward as the other alkylation reactions.^{19,36} The alkylation of the

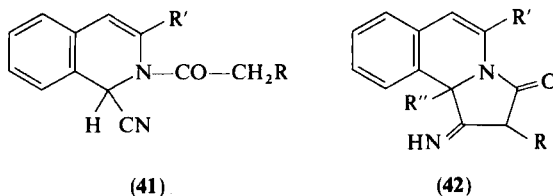
⁹² H. W. Gibson, *Macromolecules* **7**, 711 (1974).

⁹³ H. W. Gibson and F. C. Bailey, *Macromolecules* **9**, 10 (1976).

⁹⁴ H. W. Gibson and F. C. Bailey, *Macromolecules* **9**, 221 (1976).

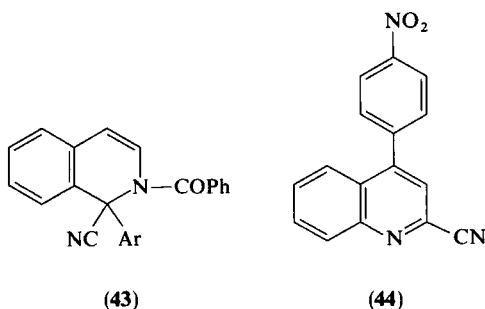
^{94a} B. C. Uff, R. S. Budhram, M. F. Consterdine, J. K. Hicks, B. P. Slingsby, and J. A. Pemblington, *J. C. S. Perkin I*, 2018 (1977).

anion of **39** is accompanied by rearrangement to give **40**.¹⁹ Rearrangement products have also been observed in other alkylations.³² Alkylation of 2-alkanoyl-1,2-dihydroisoquinaldonitriles (**41**) gives, in addition to the 1-alkyl derivatives, a set of isomers whose spectral properties are consistent with structure **42** and its tautomers.⁹⁵ 1-Cyanoisoquinolines have also been isolated in some alkylation sequences.^{28,38}



2. Reaction with Aryl Halides

Treatment of the isoquinoline Reissert compound (**2**) with sodium hydride in dimethylformamide,⁹⁶ with 50% aqueous sodium hydroxide-TEBA chloride,⁶¹ or with 50% aqueous sodium hydroxide-TBA chloride^{96a} and an activated aryl halide, such as 2,4-dinitrofluorobenzene,⁹⁶ 2-bromo-3-nitropyridine,⁹⁶ 4-nitrochlorobenzene,⁶¹ *t*-butyl 2-chloro-5-nitrobenzoate,⁶¹ 2-chloro-3-nitropyridine,^{96a} 4-chloro-3-nitropyridine,^{96a} or 9-chloroacridine^{96b} leads to the arylation product **43**. Arylation of the quinoline Reissert compound (**1**) with 4-nitrofluorobenzene in the presence of sodium hydride in dimethylformamide leads to **44**.⁹⁶ It should be noted that alkylation of



⁹⁵ H. W. Gibson, *Abstr., Am. Chem. Soc. Fall Meet.*, 1972.

⁹⁶ R. Piccirilli and F. D. Popp, *Can. J. Chem.* **47**, 3261 (1969).

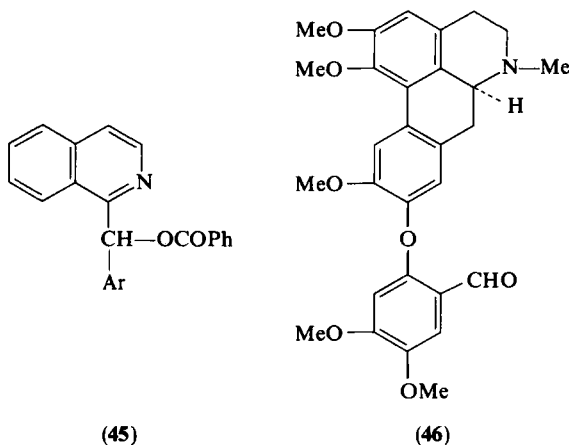
^{96a} M. Jawdosink, M. Makosza, E. Malinowska, and W. Wilczynski, *Ann. Chem. Warsaw (Transl.: Roc. Chem.)*, in press.

^{96b} W. Wilczynski, M. Jawdosink, and M. Makosza, *Roc. Chem.* **51**, 1643 (1977).

the quinoline Reissert compound also takes place in the 4-position.¹ Reaction of **2** with 50% sodium hydroxide–TBA chloride and 4-nitro-pyridine-1-oxide lead to isoquinaldonitrile, benzoic acid and 4,4'-azopyridine-*N,N'*-dioxide.^{96c}

3. Reactions with Aldehydes and Ketones

In addition to the conventional sodium hydride method of anion generation, organolithium compounds^{94,97,98} 50% aqueous sodium hydroxide in acetonitrile⁹⁹ and 50% sodium hydroxide with a phase transfer catalyst^{15a,99a} have been used to generate the anion of Reissert compounds for condensation with aldehydes. A variety of substituted benzaldehydes have been allowed to react with anions of type **26** to give **45**.^{15a,21,34,96,99,99a,100–106,106a,106b}



^{96c} M. Jawdosink, M. Makosza, E. Malinowska, and W. Wilczynski, *Ann. Chem. Warsaw* (Transl.: *Rocz. Chem.*), in press.

⁹⁷ H. W. Gibson and F. D. Popp, *Heterocycles* **2**, 5 (1974).

⁹⁸ F. D. Popp and E. Bradley Moynahan, *J. Heterocycl. Chem.* **7**, 739 (1970).

⁹⁹ A. Jonczyk, *Bull. Acad. Pol. Sdi.* **22**, 849 (1974).

^{99a} L. Castedo, J. M. Saa, R. Suau, and C. Villaverde, *Heterocycles* **9**, 659 (1978).

¹⁰⁰ E. E. Granchelli and J. L. Neumeyer, *Tetrahedron* **30**, 3701 (1974).

¹⁰¹ W. J. Houlihan and R. E. Manning, French Patent 1,587,682 (1970) [*CA* **74**, 100019 (1971)].

¹⁰² S. M. Kupchan and A. J. Liepa, U.S. Patent 3,875,167 (1975).

¹⁰³ S. M. Kupchan and A. J. Liepa, *Chem. Commun.*, 599 (1971).

¹⁰⁴ S. M. Kupchan, A. J. Liepa, V. Kameswaran, and K. Sempuku, *J. Am. Chem. Soc.* **95**, 2995 (1973).

¹⁰⁵ S. M. Kupchan and P. F. O'Brien, *J. Chem. Soc., Chem. Commun.*, 915 (1973).

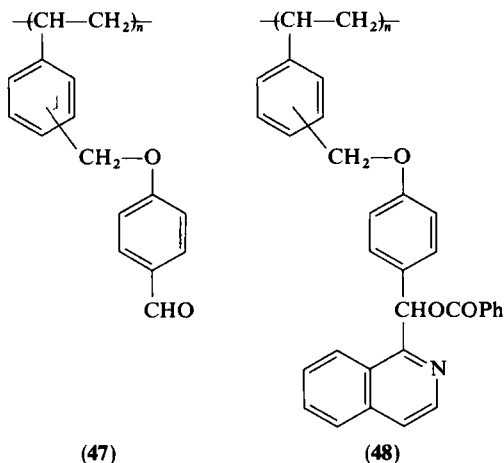
¹⁰⁶ J. L. Neumeyer and C. B. Boyce, *J. Org. Chem.* **38**, 2291 (1973).

^{106a} F. D. Popp, R. F. Watts, and R. M. Piccirilli, *Heterocycles* **9**, 669 (1978).

^{106b} P. Kerekes, G. Horvath, G. Gaal, and R. Bognar *Acta Chim. Acad. Sci. Hung.* **97**, 353 (1978).

Several of the condensations with aromatic aldehydes have been used in the synthesis of alkaloid systems.² 2-Nitrobenzaldehydes have been used in synthetic routes to 7-hydroxyaporphines,¹⁰⁰ and 2-iodobenzaldehydes have been used in oxidative photochemical routes to the aporphines and oxoaporphines caaverine, isoboldine, corunnine, and nandazurine.¹⁰⁵ The aldehyde **46** has been used with the anion of the Reissert compound derived from 6,7-dimethoxyisoquinoline in a synthesis of the alkaloid thalicarpine.¹⁰²⁻¹⁰⁴ Methyl opianate has been used with the appropriate Reissert anion to synthesize the alkaloid hydrastine.^{106b}

Polymeric aldehydes such as **47**^{107,108} and poly(vinylbenzaldehyde-co-vinylbenzaldehyde hydrate)¹⁰⁸ react with **26** to give polymers such as **48**. The anion of the quinoline Reissert compound (**1**) reacts with **47** to give a similar polymer.⁹⁴

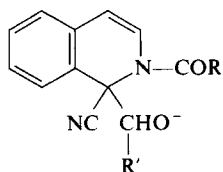


A variety of other, nonaromatic, aldehydes with **26** have also given the expected esters.^{34,48,98,99} Ferrocenecarboxaldehyde has been allowed to react with the anions of both the quinoline and isoquinoline Reissert compound.⁹⁸ Benzaldehyde³⁹ and other aromatic aldehydes⁴⁰ have been condensed with the anion of the phthalazine Reissert compound.

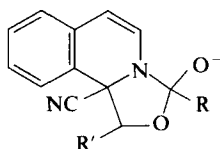
Although there is little doubt that the esters (**45**) from the condensation of aldehydes with the Reissert anion normally proceed through **49** and **50**,¹ the product **51** has been obtained together with isoquinoline from the reaction of 2-acetyldihydroisoquinaldonitrile and 2-nitrobenzaldehyde in the presence of phenyllithium.⁹⁷

¹⁰⁷ H. W. Gibson, *Macromolecules* **8**, 89 (1975).

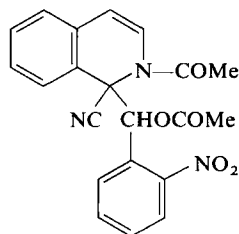
¹⁰⁸ H. W. Gibson and F. C. Bailey, *J. Polym. Sci.* **14**, 1661 (1976).



(49)

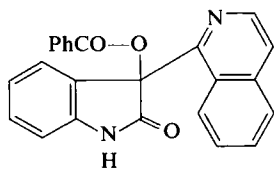


(50)

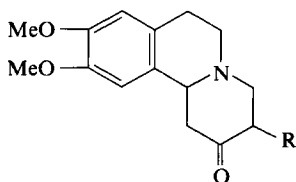


(51)

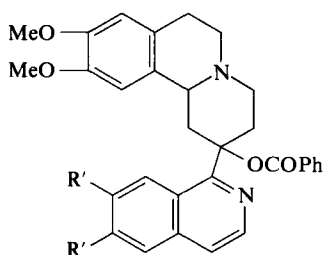
At the time of the last review¹ it was noted that the condensation of ketones with the Reissert anion was a relatively unsatisfactory reaction. It has now been shown that acetone,⁹⁹ acetophenone,⁹⁹ cyclohexanone,⁹⁹ and several *N*-substituted 4-piperidones¹⁰⁹ react with the isoquinoline Reissert compound in the presence of 50% aqueous sodium hydroxide–acetonitrile containing TEBA chloride. Isatin,^{48,106a} *N*-benzyl-3-piperidone,¹⁰⁹ and a variety of *N*-substituted 4-piperidones^{109,110} also react with isoquinoline or 6,7-dimethoxyisoquinoline Reissert compounds using sodium hydride in dimethylformamide. Thus, isatin and **2** under these conditions gives **52**.⁴⁸



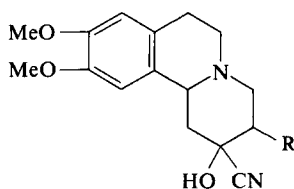
(52)



(53)



(54)



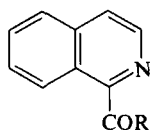
(55)

¹⁰⁹ F. D. Popp and R. F. Watts, *J. Heterocycl. Chem.* **13**, 1129 (1976).

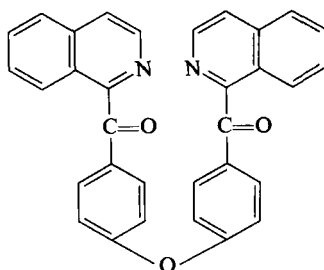
Although ketone **53** ($R=H$) reacts in a normal manner with the Reissert anion to give **54**,¹¹⁰ the reaction of **26** with **53** ($R=Me$ or Et) gives rise to the cyanohydrin **55** and 1-benzoylisoquinoline.^{110,111}

4. Rearrangements

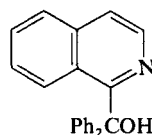
A variety of isoquinoline Reissert compounds (**2**) have been caused to undergo rearrangement of the acyl group from nitrogen to carbon by treatment with sodium hydride in dimethylformamide to give ketones of type **56**.^{18,19,21,32,34} In a similar manner, the bis-Reissert compound **14** undergoes rearrangement to **57**.³⁸ This type of rearrangement sometimes accompanies other base-catalyzed reactions.^{19,32,36,94a}



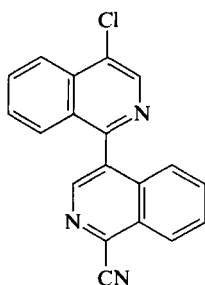
(56)



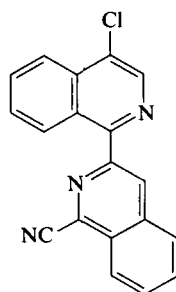
(57)



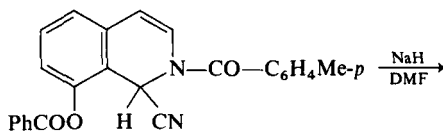
(58)



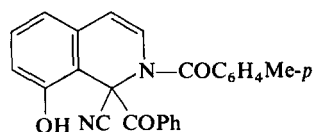
(59)



(60)



(61)



(62)

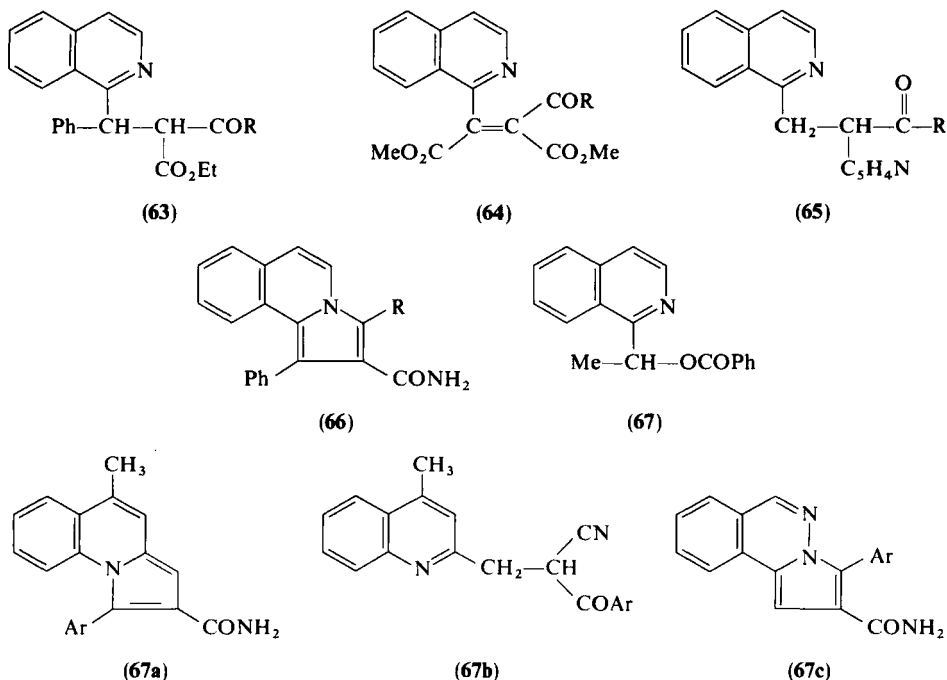
¹¹⁰ R. F. Watts and F. D. Popp, *J. Heterocycl. Chem.* **15**, 1267 (1978).

¹¹¹ R. F. Watts and F. D. Popp, *Heterocycles* **6**, 47 (1977).

Rearrangement of **26** ($R = Ph$) in phenyllithium has yielded the carbinol **58**.¹¹² Attempted rearrangement of 4-chloro-2-(4-methoxybenzoyl)dihydroisoquinaldonitrile with sodium hydride in dimethylformamide led to a product whose structure was **59** or **60**.¹⁸ Treatment of the 8-benzoyloxy-Reissert compound **61** with sodium hydride in dimethylformamide resulted in attack of the anion at the ester rather than the amide carbonyl to give **62**.³⁶

5. Other Base-Catalyzed Reactions

The anion (**26**) of the isoquinoline Reissert compound (**2**) has been used in a Michael-type reaction. Thus, reaction of **26**, generated with phenyllithium, with ethyl cinnamate and substituted cinnamates give rise to **63**,^{53,54} dimethyl acetylenedicarboxylate yields **64**,⁵³ and 2- and 4-vinylpyridines give rise to **65**.⁵⁶ Use of cinnamionitrile in this sequence leads to the isolation of **66**.^{53,54} The enol ester, vinyl acetate reacts with the isoquinoline Reissert compound in aqueous sodium hydroxide containing TEBA chloride to surprisingly give **67**.¹¹³



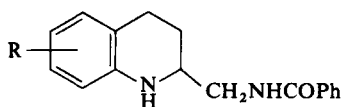
¹¹² E. Menck, A. G., British Patent 1,094,470 (1967) [*CA* **69**, 19170 (1968)].

¹¹³ M. Fedorynski, I. Gorzkowska, and M. Makosza, *Synthesis*, 120 (1977).

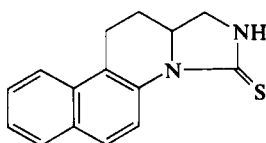
Reaction of the Reissert compound of 4-methylquinoline with sodium hydride in dimethylformamide and acrylonitrile at 0° led to rearrangement to 4-methyl-2-benzoylquinoline, while reaction at -30° led to **67a** and **67b**.^{94a} Use of sodium amide-liquid ammonia gave an improved yield of **67a** and **67b**. Reaction of **3** with potassium *t*-butoxide in dimethyl sulfoxide and acrylonitrile gave **67c**.^{113a}

C. REDUCTIONS

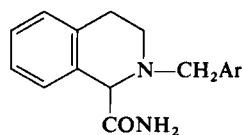
Hydrogenation of several 6- and 7-substituted quinoline Reissert compounds (**1**) in the presence of Raney nickel leads to the 2-aminomethyl-1,2,3,4-tetrahydroquinoline derivatives **68**.¹¹⁴ A similar reduction of the Reissert compound derived from benzo[*f*]quinoline, followed by reaction of the crude product with carbon disulfide, gave the diazacyclopentaphenanthrene derivative **69**.¹¹⁵



(68)



(69)



(70)

Sodium borohydride reduction of alkylated isoquinoline Reissert compounds (**27**) gives rise to 1-alkylisoquinolines (**28**) and provides an alternative to base hydrolysis for this conversion.¹¹⁶ Sodium borohydride reduction of the perchlorate salts of Reissert compounds (**19**: R = Ar, X = ClO₄) leads to the *N*-benzyl-1,2,3,4-tetrahydroisoquinolaldamides **70**.⁴⁷

D. OTHER REACTIONS

The addition of hypochlorous acid to the 3,4-position of the isoquinoline Reissert compound (**2**: R = Ph) takes place to give the chlorohydrin **71**.¹¹⁷ Use of *N*-chlorosuccinimide in ethanolic dioxane gave the *O*-ethyl derivative. Various reactions of the chlorohydrin led to isochromenes and a rearranged isoquinoline.¹¹⁷

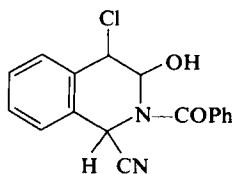
^{113a} B. C. Uff and R. S. Budhram, *Synthesis*, 206 (1978).

¹¹⁴ W. B. Wright, *J. Med. Chem.* **11**, 1161 (1968).

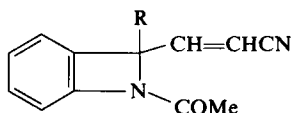
¹¹⁵ L. E. Katz and F. D. Popp, *J. Heterocycl. Chem.* **5**, 249 (1968).

¹¹⁶ I. Saito, Y. Kikugawa, and S. Yamada, *Chem. Pharm. Bull.* **22**, 740 (1974).

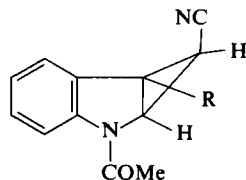
¹¹⁷ G. W. Kirby, S. L. Tan, and B. C. Uff, *Chem. Commun.*, 1075 (1969).



(71)



(72)

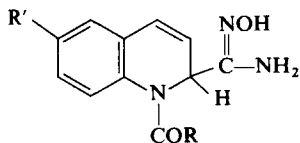


(73)

Photoisomerization of 1-acetyl-1,2-dihydroquinaldonitriles (**1**: R = Me) and the corresponding 4-methyl derivative gives **72** and **73**.¹¹⁸

Treatment of the Reissert compound derived from 4-chloroisoquinoline with phosphorus pentachloride yielded 4-chloro-1-cyanoisoquinoline.¹⁷ Similar treatment of the benzo[*f*]quinoline Reissert compound gave a mixture of nitrile and amide.¹¹⁵ The Reissert compound from 2-bromobenzo[*f*]quinoline with thionyl chloride gives 2-bromo-3-cyanobenzo[*f*]quinoline.^{118a} Oxidation of a Reissert compound in the presence of 50% sodium hydroxide and a phase transfer catalyst also gives the isoquinaldonitrile.^{118b}

The isoquinoline Reissert compound (**2**) with deuterium oxide in refluxing tetrahydrofuran gave 1-deuterioisoquinoline.¹¹⁹ The quinoline Reissert compounds (**1**: R = Ph: Me) reacted with hydroxylamine to give **74**.¹²⁰ A similar reaction also takes place in the isoquinoline series. Although **74** (R = Ph) undergoes acid-hydrolysis to give benzaldehyde, the analogous compound **74**, (R = Me) does not give any aldehyde.¹²⁰



(74)

Reaction of **2** with *p*-chlorobenzenesulfonyl azide gave only polymeric material and *p*-chlorobenzenesulfonamide.¹²¹

¹¹⁸ M. Ikeda, S. Matsugashita, F. Tabusa, H. Ishibashi, and Y. Tamura, *J. Chem. Soc., Chem. Commun.*, 575 (1975).

^{118a} Y. Mamada and M. Sugiura, *J. Pharm. Soc. Jpn.* **98**, 1081 (1978).

^{118b} S. Ruchirawat and M. Chuankamnerdkarn, *Heterocycles* **9**, 1345 (1978).

¹¹⁹ J. E. Baldwin and J. A. Duncan, *J. Org. Chem.* **36**, 627 (1971).

¹²⁰ L. R. Walters, R. C. Cook, and E. A. McFadden, *J. Chem. Eng. Data* **16**, 115 (1971).

¹²¹ A. S. Bailey, T. Morris, and Z. Rashid, *J.C.S. Perkin I*, 420 (1975).

IV. Spectral Properties

Many of the papers dealing with the synthesis and reactions of Reissert compounds routinely include spectral data. These data are consistent with the structures assigned and with previously reported spectral data for Reissert compounds. It should be noted that comparisons of data of this type was used to assign the structures **4** and **5**, which were assigned to the Reissert compounds from 1,7-¹⁰ and 1,6-naphthyridine.¹⁴ A detailed spectral study of Reissert salts²⁹ led to the assignment of structure **19**.

The mass spectra of Reissert compounds derived from quinoline, isoquinoline, and phthalazine have been discussed.¹²² The initial fragmentation involves loss of the N substituent. Additional mass spectral data have also appeared.²⁹

Proton magnetic resonance spectra of Reissert compounds have been studied.^{16,46,123,124} Particular emphasis has been given to the stereochemistry in these studies, and some tentative assignment of predominant tautomers has been made.

V. Related Compounds and Reactions

A. REDUCED AND OPEN-CHAIN ANALOGS

Reaction of the imine **75**, from 3,4-dimethoxybenzaldehyde and aminoacetal, with benzoyl chloride and potassium cyanide leads to the open-chain Reissert analog **76**.¹²⁵ This analog can be alkylated with benzyl chloride in the presence of dimethylformamide, but acid hydrolysis of the alkylation product leads to **77**.¹²⁵

Various substituted 3,4-dihydroisoquinolines have reacted with benzoyl chlorides and potassium cyanide in methylene chloride–water to give rise to so-called dihydroisoquinoline-Reissert compounds (**78**).^{29,30,47,126–131} The trimethylsilyl cyanide synthesis¹⁵ yields a dihydroisoquinoline-Reissert

¹²² F. D. Popp, K. T. Potts, and R. Armbruster, *Org. Mass Spectrom.* **3**, 1075 (1970).

¹²³ H. W. Gibson, *J. Org. Chem.* **38**, 2851 (1973).

¹²⁴ H. W. Gibson, unpublished work.

¹²⁵ S. F. Dyke and A. C. Ellis, *Tetrahedron* **27**, 3803 (1971).

¹²⁶ J. M. Bobbitt and T. Y. Cheng, *J. Org. Chem.* **41**, 443 (1976).

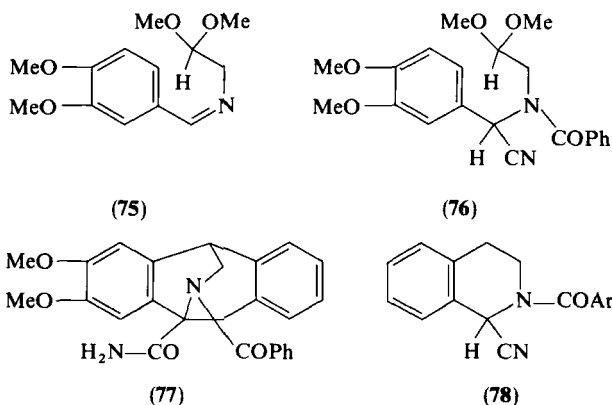
¹²⁷ H. Boehme and R. Schweitzer, *Arch. Pharm. (Weinheim)* **303**, 225 (1968).

¹²⁸ H. Boehme and K. P. Stocker, *Chem. Ber.* **105**, 1578 (1972).

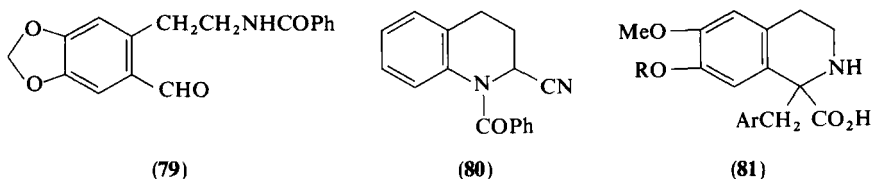
¹²⁹ S. F. Dyke, R. G. Kinsman, J. Knabe, and H. D. Holtje, *Tetrahedron*, **27**, 6181 (1971).

¹³⁰ M. Shamma and C. D. Jones, *J. Org. Chem.* **35**, 3119 (1970).

¹³¹ M. D. Rozwadowska and D. Brozda, *Bull. Acad. Pol. Sci., Ser. Sci. Chim.* **26**, 33 (1978).



compound from 6,7-dimethoxy-3,4-dihydroisoquinoline and trichloroacetyl chloride. Dihydroisoquinoline-Reissert compounds (**78**) have also been prepared from 1-cyano-1,2,3,4-tetrahydroisoquinoline.¹²⁷ The reaction of 6,7-methylenedioxy-3,4-dihydroisoquinoline with benzoyl chloride and cyanide ion led to the isolation of **79** in addition to the expected product.¹³¹ Dihydroquinoline-Reissert compounds (**80**) have been prepared by catalytic hydrogenation of the quinoline Reissert compounds (**1**) under very mild conditions.¹³²



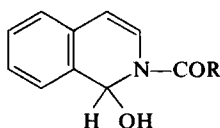
Treatment of the compounds **78** with various alkyl halides in the presence of sodium hydride results in 1-alkylation as with normal Reissert compounds.^{30,126-131} Acylation has also been reported under these conditions.^{127,128} Under a variety of conditions, however, **78** does not react with benzaldehyde.¹³¹ Acid hydrolysis of **80** gave tetrahydroquinaldic acid,¹³² while acid hydrolysis of the alkylated dihydroisoquinoline-Reissert compounds gave the amino acids **81**.^{126,130} By first complexing the alkylated dihydroisoquinoline-Reissert compound with zinc chloride in ether and then hydrolyzing the complex, the nitrile was hydrolyzed to an acid, but the amide group was left intact.¹³⁰ The perchlorate salts of dihydroisoquinoline-Reissert compounds have also been prepared,^{29,47} and sodium borohydride reduction proceeds in the same manner as reduction of the Reissert salt to

¹³² M. D. Rozwadowska, *Rocz. Chem.*, **51**, 2321 (1977).

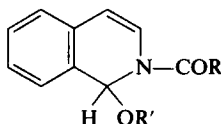
yield **70**.⁴⁷ Air oxidation of **78** under basic conditions gave isocarbo-styryl,^{118b,133} whereas a similar attempt to oxidize **80** gave only starting material.¹³³ Under these same conditions **1** and **2** gave quinaldonitrile and isoquinaldonitrile, respectively.¹³³

B. ANALOGS WITH GROUPS OTHER THAN CYANO

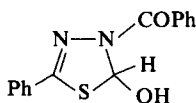
Most activity in this area has centered around the isolation of so-called pseudo-bases (**82**) in which the cyano group is replaced by a hydroxy group. Thus the pseudo-base is obtained, in addition to the normal Reissert compound, from 5-nitroisoquinoline,^{37,134} 3-methyl-5-nitroisoquinoline,³⁷ 6-nitroquinoline,³⁷ and phthalazine.^{11,12} Heating the pseudo-bases in alcohol gives rise to the ethers **83**. A discussion of some of the chemistry and properties of the pseudo-bases has appeared.³⁷ The formation of the pseudo-bases can be suppressed and that of the Reissert compounds increased by the use of a phase-transfer catalyst.^{11,12} Pseudo-bases have also been obtained in attempts to form Reissert compounds from 1,6-naphthyridine⁷ and 4,6-phenanthroline.^{42,135} 2-Phenyl-1,2,3-thiadiazole and benzoyl chloride in the presence of cyanide gave **84**¹³⁶ and imidazo[1,5-*a*]pyrazines with acid chloride gave **85**¹³⁷ in reactions analogous to the pseudo-base formation.



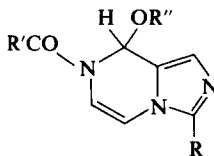
(82)



(83)



(84)



(85)

¹³³ M. D. Rozwadowska and D. Brozda, *Tetrahedron Lett.*, 589 (1978).

¹³⁴ B. C. Uff, J. R. Kershaw, and S. R. Chhabra, *Tetrahedron Lett.*, 1678 (1969).

¹³⁵ F. D. Popp and D. K. Chesney, unpublished work (1971).

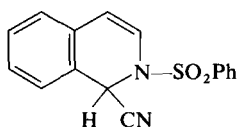
¹³⁶ A. Alemagna and T. Bacchetti, *Gazz. Chim. Ital.* **102**, 1068 (1972).

¹³⁷ E. Abushanab, D. Y. Lee, and L. Goodman, *J. Org. Chem.* **40**, 3376 (1975).

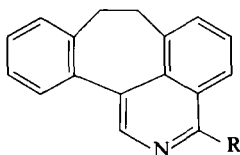
C. ANALOGS WITH GROUPS OTHER THAN ACYL

1. *N*-Arylsulfonyl Compounds

The main interest in compound **86** stems from the earlier report¹ of its conversion into 1-cyanoisoquinoline. Thus, hydrolysis of **86** with potassium hydroxide in dimethylformamide at 20°¹⁸ or treatment with sodium borohydride in ethanol¹¹⁶ gave 1-cyanoisoquinoline. This conversion takes place in the presence or in the absence of oxygen.¹³³ Use of 50% sodium hydroxide with **86** gave the 1-amide.¹³⁸ This procedure has also been used to prepare 1-cyanophthalazine,³⁹ 5-cyano-1,6-naphthyridine,⁷ and **87** from **88** via **89**.^{139,140}

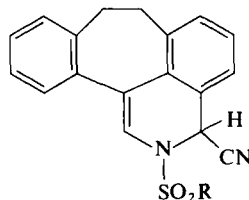


(86)

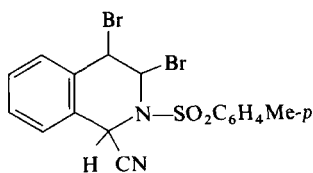


(87) R = CN

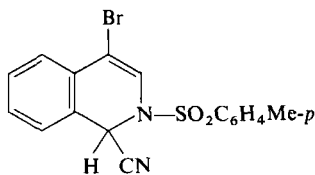
(88) R = H



(89)



(90)



(91)

The 2-*p*-toluenesulfonyl analog of **86** is brominated with bromine in chloroform to give **90**.¹⁴¹ Reactions of **90** include treatment with morpholine, to give **91** or 4-bromoisoquinaldonitrile depending upon conditions.¹⁴¹

Isoquinoline reacts with potassium cyanide and sulfuryl chloride to give, depending on reaction conditions, a number of products including 4-chloro-1-cyanoisoquinoline.¹⁷ These are believed to be formed via an intermediate of type **86**, in which Ph is replaced by Cl.

¹³⁸ L. E. Katz and F. D. Popp, *J. Heterocycl. Chem.* **4**, 635 (1967).

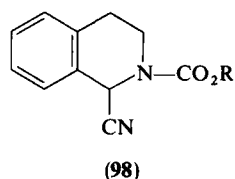
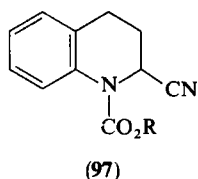
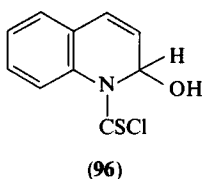
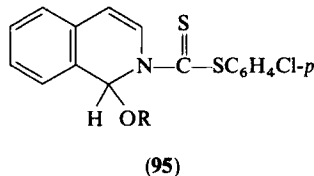
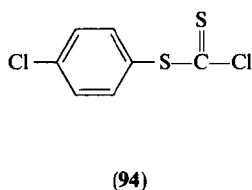
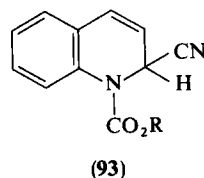
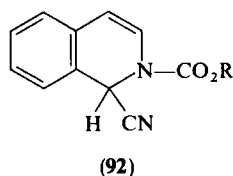
¹³⁹ L. G. Humber, M. A. Davis, G. Beaulieu, and M. P. Charest, *Can. J. Chem.* **46**, 2981 (1968).

¹⁴⁰ L. G. Humber and M. A. Davis, U.S. Patent 3,403,155 (1968).

¹⁴¹ T. George, D. V. Mehta, and D. A. Dabholkar, *J. Org. Chem.* **39**, 1965 (1974).

2. *N*-Alkoxycarbonyl Compounds

The unpublished results in this area that were noted in the earlier review¹ have now been published.^{135,142} Reaction of isoquinolines,¹⁴² quinolines,^{115,142,143} and phthalazine³⁹ with chloroformates and cyanide ion in methylene chloride–water gives rise to **92**, **93**, and the related phthalazine derivative, respectively. Phase-transfer catalysis has also been used in this series.¹² A similar reaction takes place between quinoline¹⁴⁴ and isoquinoline^{144,145} and thiocarbonyl chlorides¹¹ and between a chlorothioformate¹⁴² and isoquinoline, but use of the dithio compound **94** with isoquinoline and cyanide ion gave only the pseudo-base **95** and its ether.¹⁴⁵ A similar reaction, leading through an intermediate **96**, has been proposed for the reaction of quinoline, potassium cyanide, and thiophosgene.¹⁴⁴



Some dihydro-Reissert analogs have been prepared in this series. Thus, catalytic hydrogenation of **93** under very mild conditions¹³² or an ionic hydrogenation of **92** using triethylsilane and trifluoroacetic acid¹³¹ gives **97** and **98**, respectively. The dihydro analog **98** has also been prepared from 3,4-dihydroisoquinoline¹³¹ and from 1-cyano-1,2,3,4-tetrahydroisoquinoline.¹²⁷

¹⁴² F. D. Popp, L. E. Katz, C. W. Klinowski, and J. M. Wefer, *J. Org. Chem.* **33**, 4447 (1968).

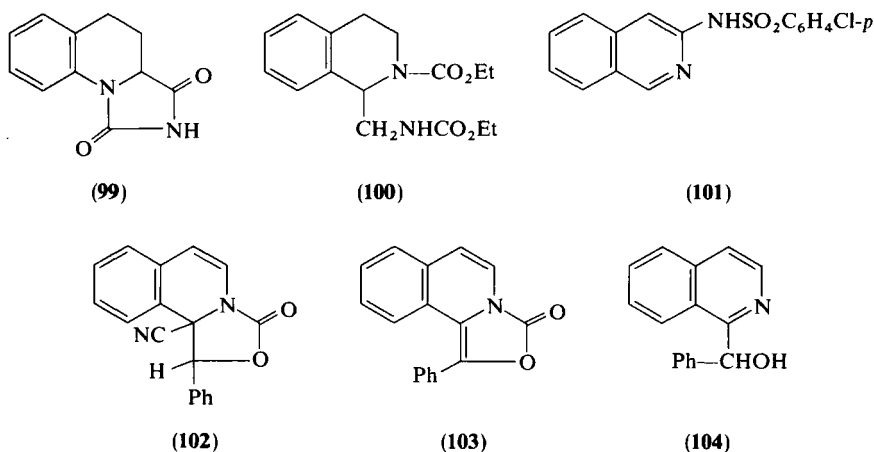
¹⁴³ E. O. Snoko and F. D. Popp, *J. Heterocycl. Chem.* **10**, 99 (1973).

¹⁴⁴ R. Hull, *J. Chem. Soc. C*, 1777 (1968).

¹⁴⁵ F. D. Popp and C. W. Klinowski, *J. Chem. Soc. C*, 741 (1969).

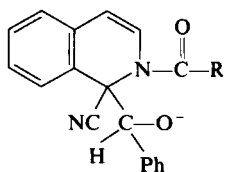
Alkylation of **92** takes place in the same manner as alkylation of **2**.¹⁴² Acid hydrolysis of **92** gives isoquinoline,¹⁴² and acid hydrolysis of the reduced analog **98** converts the nitrile into an amide.¹³¹ In contrast, acid hydrolysis of the reduced quinoline **97** converts the nitrile into a carboxylic acid.¹³² Air oxidation of **98** in the presence of base gives isocarbostryl,^{118b,133} and similar treatment of **92** gives isoquinaldonitrile.¹³³ In contrast, **97** does not react under these conditions, but **93** gives quinaldonitrile.¹³³

Base hydrolysis of **97** gives the ureide **99**.¹³² Hydroxylamine converts the nitrile into an amidoxime in both **92**¹⁴² and **93**¹⁴³. The similar reaction of the benzo[*f*]quinoline analog of **93** with hydroxylamine gives a complex mixture of products including a double-bond isomer.¹⁴² Although **97** was prepared by mild catalytic hydrogenation of **93**,¹³² catalytic hydrogenation of **92** at 4 atmospheres gave **100**.¹³⁵ This intermolecular rearrangement on reduction is analogous to that reported for normal Reissert compounds. A similar reduction takes place with the benzo[*f*]quinoline analog.¹¹⁵ Treatment of **92** with *p*-chlorobenzenesulfonyl azide gives a small amount of **101**.¹²¹

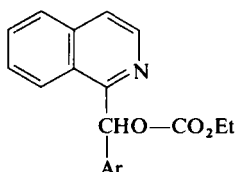


Reaction of **92** with benzaldehyde in the presence of butyllithium gave **102**; use of sodium hydride in dimethylformamide gave **103** and **104**.¹⁴² The ester of **104** is the product obtained from the reaction of the anion of a normal Reissert compound (**2**) with benzaldehyde, and both reactions must proceed through an intermediate of type **105**. Compounds of type **103** have also been prepared from **104**.¹⁰⁶ Reaction of the quinoline analog (**93**) with benzaldehyde leads to the quinoline analogs of **102** and **103**.¹⁴³ Reaction of **92** with aromatic aldehydes in the presence of 50% sodium hydroxide-benzene containing TEBA chloride gave alcohols of type **104** and carbonate of type **106**.¹⁴⁶ Reaction of the dihydroisoquinoline analogs (**98**) gave

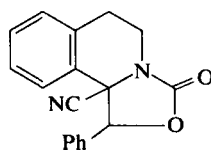
products of type **107** that are analogous to one of the products (**102**) from the compounds **92**.^{131,146} Under similar conditions the dihydroquinoline analog (**97**) does not react with aldehydes, and in fact it does not undergo deuterium exchange under basic conditions.¹³²



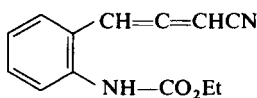
(105)



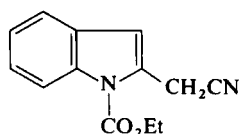
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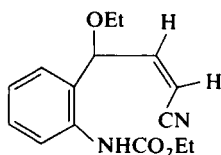
(107)



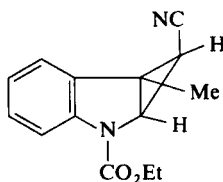
(108)



(109)



(110)



(111)

Irradiation of a series of ethyl 2-cyano-1,2-dihydroquinoline-1-carboxylates (**93**; R = Et) gave allenic compounds (**108**), which are readily transformed into indoles (**109**).^{147,148} When the irradiation was carried out in ethanol, **109** and the ethanol adducts **110** were obtained.^{147,148} When **93** contained a 4-methyl substituent irradiation in ether gave the 3-methyl analog of **109** and the cycloprop[*b*]indole **111** (cf. **73**; see Section III,D).^{149,150} Other 4-substituted derivatives of **93** give analogs of **111**, and 3,4-disubstituted derivatives give analogs of **111** and also the corresponding exo-

¹⁴⁶ M. D. Rozwadowska, *Can. J. Chem.* **55**, 164 (1977).

¹⁴⁷ M. Ikeda, S. Matsugashita, H. Ishibashi, and Y. Tamura, *J. Chem. Soc., Chem. Commun.*, 922 (1973).

¹⁴⁸ M. Ikeda, S. Matsugashita, and Y. Tamura, *J.C.S. Perkin I*, 2587 (1976).

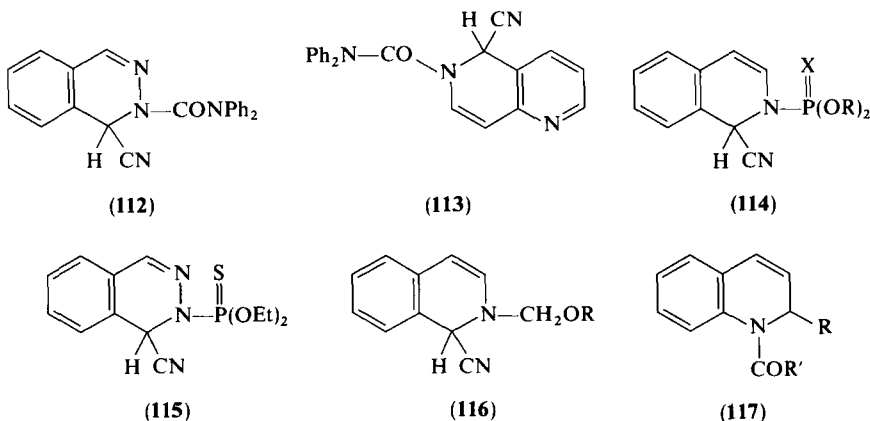
¹⁴⁹ M. Ikeda, S. Matsugashita, F. Tabusa, H. Ishibashi, and Y. Tamura, *J. Chem. Soc., Chem. Commun.*, 433 (1974).

¹⁵⁰ M. Ikeda, S. Matsugashita, F. Tabusa, and Y. Tamura, *J.C.S. Perkin I*, 1166 (1977).

isomers.¹⁵⁰ Further mechanistic studies of these transformations have appeared.^{150a} These cycloprop[*b*]indoles have been used as intermediates in the synthesis of the physostigmine ring system.¹⁵¹

3. Miscellaneous Analogs

Reaction of *N,N*-diphenylcarbamoyl chloride and cyanide ion with phthalazine³⁹ and 1,6-naphthyridine⁷ gave the compounds **112** and **113**, respectively.



The paper reporting the reaction of isoquinoline and potassium cyanide with dialkyl chlorophosphates and dialkyl chlorothiophosphates to give products of the type **114**¹ has now appeared.¹⁵² These compounds can be alkylated in the same manner as a normal Reissert compound, and hydrolysis of the alkylation product gives 1-methylisoquinoline.¹⁵² A phthalazine analog (**115**) has also been prepared.³⁹

A number of other miscellaneous systems that bear some relationship to Reissert compounds have also been reported but will not be covered in depth here. Thus, for example, the reaction of isoquinoline, potassium cyanide, and alkyl chloromethyl ethers give **116**.¹⁵³ A similar compound was also prepared from quinoline.¹⁵³ Compounds of type **117** have been reported to undergo rearrangements similar to Reissert compounds.¹⁵⁴ A

^{150a} M. Ikeda, S. Matsugashita, and Y. Tamura, *Heterocycles* **9**, 281 (1978).

¹⁵¹ M. Ikeda, S. Matsugashita, and Y. Tamura, *J.C.S. Perkin I*, 1770 (1977).

¹⁵² D. M. Spatz and F. D. Popp, *J. Heterocycl. Chem.* **5**, 497 (1968).

¹⁵³ H. Boehme and R. Schweitzer, *Chem. Ber.* **102**, 3606 (1969).

¹⁵⁴ C. E. Crawforth and O. Meth-Cohn, *J. Chem. Soc., Chem. Commun.*, 865 (1972).

number of 1-cyanoisochromans¹⁵⁵ and 1-cyanoisothiochromans^{155,156} have been prepared, and their alkylation, acylation, and arylation has been studied. Finally, Sheinkman and co-workers have reported the reaction of a wide variety of C—H acidic compounds with *N*-acyl salts of isoquinoline.¹⁵⁷

Note Added in Proof

A Reissert compound has been prepared from 9-methoxyellipticine and both it and **10** give a fluoroborate salt of the type **19**.¹⁵⁸ The Reissert compound of 6,7-dimethoxyphthalazine has been used to prepare an azapapaverine.^{15b} The oxoaporphine alkaloid subessiline has been synthesized using the Reissert compound of 5,6,7-trimethoxyisoquinoline.¹⁵⁹ The reaction of vanillin Schiff bases with benzoyl cyanide yields open-chain analogs of Reissert compounds.¹⁶⁰ α -Acylaminonitriles, which can be considered as open-chain Reissert compounds, have been converted to open-chain analogs of Reissert salts (5-imino-3,5-dihydrooxazole derivatives).^{161,162}

¹⁵⁵ H. Boehme, K. Lindenberg, R. Priesner, and B. Unterhalt, *Arch. Pharm. (Weinheim)* **301**, 326 (1968).

¹⁵⁶ H. Boehme and U. Sitorus, *Phosphorus Sulfur* **1**, 129 (1976).

¹⁵⁷ A. K. Sheinkman, *Usp. Khim.* **42**, 1415 (1973).

¹⁵⁸ S. Veeraraghavan and F. D. Popp, Unpublished results, 1978–1979.

¹⁵⁹ J. W. Skiles and M. P. Cava, *J. Org. Chem.* **44**, 409 (1979).

¹⁶⁰ M. Rai, K. Krishan, and A. Singh, *Indian. J. Chem. B* **16**, 834 (1978).

¹⁶¹ S. Sato, T. Mase, and M. Ohta, *Bull. Chem. Soc. Jap* **41**, 2218 (1968).

¹⁶² P. Roesler and J. P. Fleury, *Bull. Soc. Chim. Fr.* **2**, 631 (1968).

Current Views on Some Physicochemical Aspects of Purines

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I. Introduction

Since the original article¹ appeared some 12 years ago, considerable advances in many areas of purine chemistry have been made. These have come about largely through the widespread use of new instrumental techniques, notably nuclear magnetic resonance (NMR), electron spin resonance (ESR), and mass spectrometry, which allow structural features and other physical data to be determined rapidly and mechanisms of ongoing reactions to be studied *in situ*. For these reasons it is impossible, within the limits imposed, to update all the sections in the original work. This disadvantage, however, is partly overcome by the fact that in the intervening period a variety of specialist articles and reviews on purines have appeared, mostly of recent origin, dealing *inter alia* with tautomerism and prototropy,²

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¹ J. H. Lister, *Adv. Heterocycl. Chem.* **6**, 1 (1966).

² J. Elguero, C. Marzin, A. R. Katritzky, and P. Linda, *Adv. Heterocycl. Chem., Suppl.* **1**, 502 (1976).

electronic aspects and structure,³ proton⁴ and carbon-13⁵ magnetic resonance spectra, and nucleophilic and electrophilic reactions.⁶ The strategy adopted for this monograph has been, therefore, to concentrate on particular topics of current interest that have not been covered comprehensively elsewhere. As a basis for selection, the subjects chosen come under the heading either of new topics, i.e., those that have come into being since 1966 or those that have grown in importance since that date. Some indication of the change in emphasis can be seen in the fact that in the original work about 75% of space was devoted to nucleophilic substitution, only passing mention being made of electrophilic attack at a carbon atom, whereas in the current article the reverse holds for the amounts of subject matter devoted to these two areas.

In general, coverage is based upon work published during or after 1970, as prior to this purine chemistry is extensively covered by a major work⁷ and a lengthy review⁸ of slightly earlier date.

II. The Ring System

A. THEORETICAL CONSIDERATIONS

Attempts to correlate results of CNDO/2 or MINDO type calculations with physical parameters or positional chemical reactivity continue. The rationalization made regarding the overall electron disposition in the purine ring system has been questioned. Originally the overall effect was taken to arise from annelation of a π -electron-excessive imidazole ring with a π -electron-deficient pyrimidine moiety.⁹ Charge distribution calculations (CNDO type) carried out with the four possible protomers of purine (1H (1a) and 3H (2a) tautomers, depicted in classical valence terms as the respective para and ortho quinonoid forms, the converse seems to hold in the case of both the 7H (3a) and 9H (4a) isomers where the imidazole ring is now accommodating the positive π -charge with the pyrimidine fragment π -

³ B. Pullman and A. Pullman, *Adv. Heterocycl. Chem.* **13**, 77 (1971).

⁴ L. B. Townsend, *Syn. Proc. Nucleic Acid Chem.* **2**, 313 (1973).

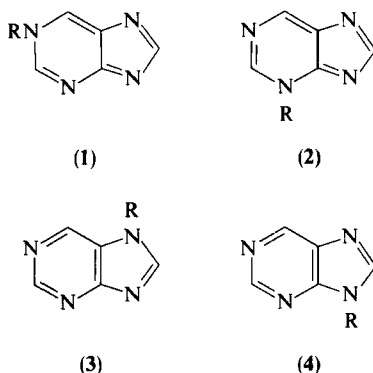
⁵ M. C. Thorpe, W. C. Coburn, and J. A. Montgomery, *J. Magn. Reson.* **6**, 98 (1974).

⁶ F. Bergmann, D. Lichtenberg, U. Reichman, and Z. Neiman, *Jerusalem Symp. Quant. Chem. Biochem.* **6**, 397 (1974).

⁷ J. H. Lister, "Purines," Wiley (Interscience), New York, 1971.

⁸ R. K. Robins, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 8, p. 162. Wiley, New York, 1967.

⁹ A. Albert, "Heterocyclic Chemistry," 2nd Ed. Oxford Univ. Press, (Athlone), London and New York, 1968.



a: R = H
b: R = Me

negative.¹⁰ These contrasting states are reflected in MINDO-calculated heats of formation that show exothermic values for the 7H (**3a**) and 9H (**4a**) forms and endothermic values for the corresponding 1H (**1a**) and 3H (**2a**) structures. Orders of stability agree with those found by other methods with 9H > 7H and 3H > 1H, the greater stability being shown by the former pair, of which the 9H protomer exhibits the highest stability of all.¹¹ The same order is obtained from modified CNDO calculations of energy values where the sequence 9H < 7H < 3H < 1H obtains.¹² Such results are in line with observations that, while purine, owing to interbase hydrogen bonding, is present in the crystal as the 7H tautomer (**3a**), in solution averaging occurs to produce a 7H/9H protomer mixture.¹² Energy differences between the four structures are also illustrated by comparison of the magnetic circular dichroism (MCD) spectra of the homologous *N*-methylpurines.¹³ The MCD bands for the 1- (**1b**) and 3-methyl (**2b**) derivatives are of lower intensity and at lower wavelengths than are the corresponding bands in the 7- (**3b**) and 9-methylpurine (**4b**) spectra. A further and significant difference between the two pairs of purines is seen following protonation in that the first MCD bands of the 1- and 3-methyl derivatives are blue shifted (15–20 nm) whereas a red displacement (6–10 nm) occurs with the 7- and 9-methyl analogs. In addition, protonation alters peak intensities and the variation can be used to identify a particular isomer. Thus, while the band due to 3-methylpurine undergoes a 3-fold intensification, the 1-methyl analog suffers only a 0.25-fold

¹⁰ Z. Neiman, *Experientia* **31**, 996 (1975).

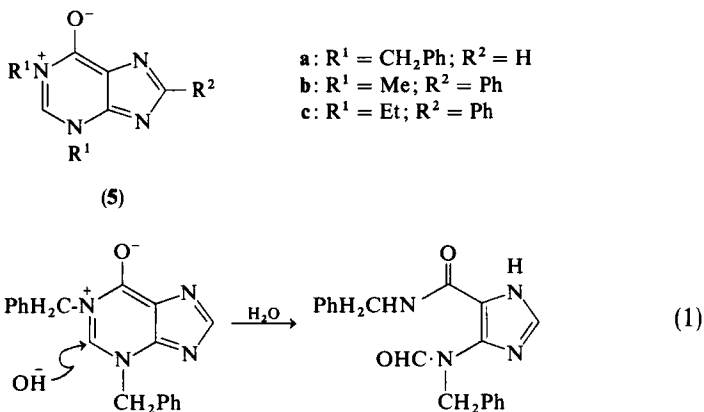
¹¹ Z. Neiman, *J.C.S. Perkin II*, 585 (1972).

¹² M. Kamiya and Y. Akahori, *Chem. Pharm. Bull.* **21**, 1470 (1973).

¹³ L. B. Townsend, D. W. Miles, S. J. Manning, and H. Eyring, *J. Heterocycl. Chem.* **10**, 419 (1973).

increase. By contrast, the 9-methyl isomer suffers a 3-fold decrease in band intensity whereas only a 0.25-fold reduction in band height is noted with the 7-methyl derivative.¹³

The fixed bond arrangement of the betainoid hypoxanthine derivatives (5)¹⁴ can be related to that present in 1- and 3-alkylpurines. The negative character (π -electron excessive) of the five-membered ring is shown by the highfield shift of the 8H signal ($\delta 7.70$) and the more basic nature ($pK_a \sim 5.2$) shown by **5a** in contrast to the corresponding shifts ($\delta 7.8$ – 7.9) and pK_a (2.1–2.6) given by covalent mono- and dimethylhypoxanthines. No fundamental disparity is found in the data derived from molecular orbital treatment of the two ring systems; the main difference lies in the lower energy values existing between the highest occupied and the lowest empty orbitals in the mesoionic structures. Although a fairly large charge separation occurs in the latter, only low polar character is observed.¹⁵ Localization of the positive charge in the pyrimidine fragment, however, is indicated by ring opening, which occurs slowly in water owing to hydroxyl ion attack at the 2-position [Eq. (1)]. Other examples of this type of ring fission induced by nucleophilic attack are known.¹⁶



B. N7–N9 PROTOTROPY

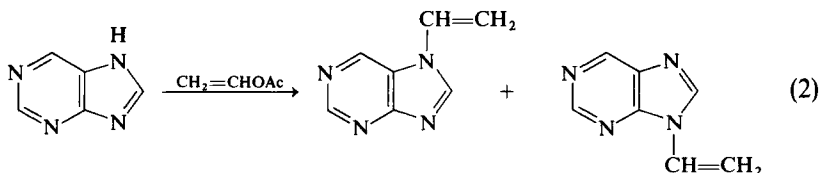
This important aspect of purine structure is still of active interest. Theoretical and practical studies have been carried out to ascertain the site of

¹⁴ R. A. Coburn and R. A. Carapelloti, *Tetrahedron Lett.*, 663 (1974).

¹⁵ R. A. Coburn, R. A. Carapelloti, and R. A. Glennon, *J. Heterocycl. Chem.* **10**, 479 (1973).

¹⁶ J. A. Montgomery, K. Hewson, S. J. Clayton, and H. J. Thomas, *J. Org. Chem.* **31**, 2202 (1966); Z. Neiman, *J. Chem. Soc. C*, 91 (1970).

the labile hydrogen atom. The major difficulty in mathematical treatment lies in finding a formalism that can take into account all vital intrinsic and environmental parameters¹⁷; the results obtained usually reflect only ground-state values¹⁸ of the molecule in which the effects of extraneous factors, e.g., solvent, are not allowed for. With purine itself, total energy values, derived from CNDO calculations, indicate the 7H protomer to have a slightly lower energy value than the 9H analog. While this assignment appears to be correct for the solid state,¹⁹ in solution^{12,20} the virtual equivalence of reactivity and energy between N-7 and N-9 has been practically demonstrated. Thus, when purine is treated with vinyl acetate, equal amounts of 7- and 9-vinylpurine are obtained [Eq. (2)].²¹ Studies with other purines demonstrate that this reaction is kinetically rather than thermodynamically controlled and in nearly every case affords only one alkylated product, the alkyl group replacing the most labile proton in the molecule.²¹



Further support for the existence in solution of near equal amounts of the 7H and 9H protomers of purine is provided by carbon-13 resonance data in which the disposition of the acidic proton can be correlated with the magnitude of the shift changes of the C-4 and C-5 bridgehead atoms.²² Use of the 7- and 9- methyl homologs as reference compounds and extrapolation of the results to the 7H and 9H purines by applying α - and β -substituent parameter corrections gives 40% for the 7H tautomer in dimethyl sulfoxide²³ and an estimate of 58% in water.²⁴ Data obtained from a temperature-jump relaxation technique used to study the rapid kinetics of $7H \rightleftharpoons 9H$ prototropy of adenine in aqueous solution has given values for the equilibrium constant ($K = C_{7H}/C_{9H} = 0.28$ at 20°) and the 7H isomer population ($\sim 22\%$).²⁵ This

¹⁷ Z. Neiman, *Isr. J. Chem.* **10**, 819 (1972).

¹⁸ S. P. Gupta and P. Singh, *Indian J. Chem.* **13**, 668 (1975).

¹⁹ D. J. Watson, R. M. Sweet, and R. Marsh, *Acta Crystallogr., Sect. B* **19**, 573 (1965).

²⁰ F. Jordan and H. D. Sostman, *J. Am. Chem. Soc.* **94**, 7898 (1972).

²¹ J. Pitha, *J. Org. Chem.* **40**, 3296 (1975).

²² R. J. Pugmire and D. M. Grant, *J. Am. Chem. Soc.* **93**, 1880 (1971).

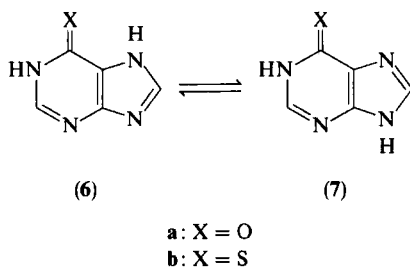
²³ M. T. Chenon, R. J. Pugmire, D. M. Grant, R. P. Panzica, and L. B. Townsend, *J. Am. Chem. Soc.* **97**, 4627 (1975).

²⁴ M. T. Chenon, R. J. Pugmire, D. M. Grant, R. P. Panzica, and L. B. Townsend, *J. Am. Chem. Soc.* **97**, 4636 (1975).

²⁵ M. Dreyfus, G. Dodin, O. Bensaude, and J. E. Dubois, *J. Am. Chem. Soc.* **97**, 2369 (1975).

figure compares well with a value of 15% obtained from the ^{13}C spectral determination of adenine in dimethyl sulfoxide.²⁴ Both results, however, support the thesis that the 9H form predominates in solution. Acid and base catalyze the rate of prototropic exchange in aqueous media, either hydroxyl ion or the adenine anion serving as basic catalysts. Line broadening in the NMR spectra due to averaging has been cited as evidence for $7\text{H} \rightleftharpoons 9\text{H}$ prototropy. In ^1H -NMR spectra this shows in the imidazole imino group signal,^{26,27} whereas in the ^{13}C -NMR spectra the signals most affected are those due to the C-4 and C-5 bridgehead atoms.^{5,24} This technique has been applied to resolve more complex tautomers and shows that hypoxanthine is slightly more favored as the 7H tautomer (**6a**) than the 9H protomer (**7a**), in the ratio 58%:42%. Corresponding figures for the 6-mercaptapurine analog show a more diverse trend but again the 7H form (**6b**) is the major (79%) component.²⁴

Although the protomer distribution values for the latter are at variance with those obtained from UV spectral studies,²⁸ no rationale to account for



the discrepancy has been advanced. Comparisons of charge localizations in 7- and 9-methylpurines, which resemble those of the parent 7H and 9H analogs, have also provided support for the above protomeric status.²⁹ ESR spectral investigation of the radical anion of purine, produced by low temperature (-34 to -55°) electrolysis of a dimethylformamide solution, showed a major and minor radical component present. From correlations between observed and calculated hyperfine splittings the main product is claimed to be the 9H purine radical, the minor one being the 7H analog.³⁰ A similar radical protomer mixture is found when 6-cyanopurine is treated likewise.³⁰

²⁶ L. M. Twanmoh, H. B. Wood, and J. S. Driscoll, *J. Heterocycl. Chem.* **10**, 187 (1973).

²⁷ T. H. Marshall and E. Grunwald, *J. Am. Chem. Soc.* **91**, 4541 (1969).

²⁸ D. Lichtenberg, F. Bergmann, and Z. Neiman, *Isr. J. Chem.* **10**, 805 (1972).

²⁹ R. J. Pugmire, D. M. Grant, L. B. Townsend, and R. K. Robins, *J. Am. Chem. Soc.* **95**, 2791 (1973).

³⁰ M. D. Sevilla, *J. Phys. Chem.* **74**, 805 (1970).

C. CRYSTALLOGRAPHIC STUDIES

From the X-ray crystal analyses of a number of purines examined during the past decade, a significant feature that emerges is the lack of planarity between the five- and six-membered rings about the C4—C5 bond, a dihedral angle between 0.5° and 1.0° being usual. In virtually every case the imidazole ring shows complete planarity, but the pyrimidine moiety and associated substituent groups exhibit out of plane features. Bond lengths and, therefore, associated bond angles, vary with the ionic state. An illustration is the difference in bond angles in the imidazole ring between the mono-³¹ and the dication³² of adenine. The variation is ascribed to delocalization of the electron density in the latter ion because of the second protonation occurring at N-7. With 7-methyladenine dihydrochloride, protonation sites are located at N-3 and N-9 and this affords the first direct evidence for protonation at N-3 in adenines.³³ The structural details of 3-ethyladenine were in good agreement with those of the 9-alkylated derivative. In the crystal, pairs of molecules are linked by hydrogen bonds between the exocyclic amino group and the 7-nitrogen.³⁴ Confirmation that both hypoxanthine³⁵ and 6-mercaptapurine^{36,37} exist solely as the 7H lactam tautomers (**6a** and **6b**) in the solid state is available. Only minor structural differences are found between the oxygen and sulfur analogs. The monocation of hypoxanthine has hydrogen atoms located at N-1, N-7, and N-9, the last being the site of protonation.³⁵ A relatively large dihedral angle (1.16°) occurs between the ring planes in 6-mercaptapurine, this being accompanied by a significant out-of-plane deformation (1.5°) of the carbon-sulfur bond.³⁶ Pronounced buckling of the pyrimidine ring occurs at the 2-carbon in 1,3,9-trimethylxanthine (isocaffeine) with out-of-plane displacement of the attached carbonyl bond.³⁸ With xanthine, examined as the anionic form (sodium salt), hydrogen was found to be lacking at N-3 and N-7. This result is accommodated by the canonical structures **8**.³⁹ The 9H tautomer is noteworthy as in solution the acidic proton in the imidazole ring is usually assigned to N-7. The disposition of 9-ethylguanine in the hydrochloride salt crystal is unusual in showing a hemihydrochloride state, the unit being composed of

³¹ T. J. Kistenmacher and T. Shigematsu, *Acta Crystallogr., Sect. B* **30**, 166 (1974).

³² T. J. Kistenmacher and T. Shigematsu, *Acta Crystallogr., Sect. B* **30**, 1528 (1974).

³³ T. J. Kistenmacher and T. Shigematsu, *Acta Crystallogr., Sect. B* **31**, 211 (1975).

³⁴ C. S. Petersen and S. Furberg, *Acta Chem. Scand., Ser. B* **29**, 37 (1975).

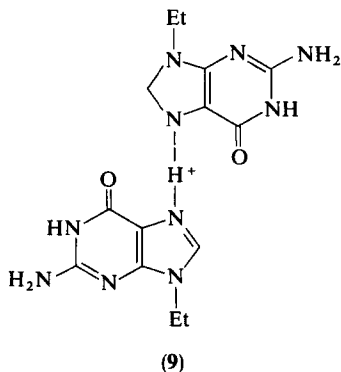
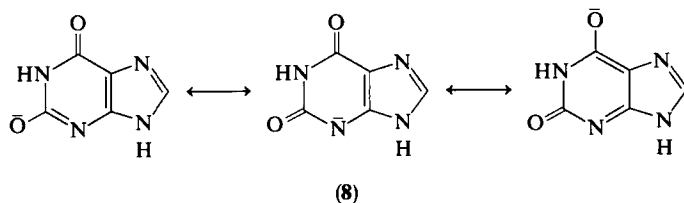
³⁵ J. Sletten and L. H. Jensen, *Acta Crystallogr., Sect. B* **25**, 1608 (1969).

³⁶ G. M. Brown, *Acta Crystallogr., Sect. B* **25**, 1338 (1969).

³⁷ E. Sletten, J. Sletten, and L. H. Jensen, *Acta Crystallogr., Sect. B* **25**, 1330 (1969).

³⁸ H. Rasmussen and E. Sletten, *Acta Chem. Scand.* **27**, 2757 (1973).

³⁹ H. Mizuno, T. Fujiwara, and K. Tomita, *Bull. Chem. Soc. Jpn.* **42**, 3099 (1969).



an asymmetric pair of bases (9), one of which is the protonated form. Hydrogen bonding provides the binding force between the 7-positions, and the bond is distinctive in being the shortest one (2.637 Å) observed to date. In spite of the associated positive charges, the units show close stacking.⁴⁰

III. The Nucleophilic Nature of the 8-Position

The wide range of reactions found to occur at the 2-, 6-, and 8-carbon atoms reflects the essentially electrophilic character of these positions. However, the 8-position differs from the other two in showing also a pronounced nucleophilic disposition in certain derivatives, notably those having one, or better more than one, electron-donating groups. In such purines the electron density of the 8-carbon is enhanced and may therefore approach that of the analogous 2-carbon atom in imidazoles. This rationalization is an oversimplification, as purines having a variety of substituents show some degree of nucleophilic character at C-8. Among the electrophiles that have been involved are hydrogen isotope ions, hydrogen radicals, alkyl radicals, and alkyl cations. This aspect of purine chemistry has relevance to the study of mechanisms of carcinogenesis⁴¹ in view of the interactions observed between aromatic carcinogens and DNA, in which the purine bases, guanine,

⁴⁰ G. S. Mandel and R. E. Marsh, *Acta Crystallogr., Sect. B* **31**, 2862 (1975).

⁴¹ J. A. Miller, *Cancer Res.* **30**, 559 (1970).

and to a lesser extent adenine, form covalently linked carcinogen-purine adducts through the 8-position of the latter.⁴²

A. HYDROGEN EXCHANGE

Exchange reactions between hydrogen, deuterium, or tritium located at C-8 have been examined in a wide variety of purines and their derivatives which include the parent member,^{43,44} adenine,^{45,46} guanosine,^{47,48} hypoxanthine,⁴⁸⁻⁵⁰ xanthine,⁵¹ 6-chloropurine,⁴⁶ 6-mercaptopurine,^{46,49} and others.^{46,49}

The application of proton resonance techniques to deuterated derivatives enables qualitative and quantitative observations of the hydrogen exchange process. With tritium-labeled bases the gain in radioactivity of the protic solvent provides a convenient means of monitoring the reaction course. The comparative ease with which either deuterium or tritium can be inserted at the 8-position, compared with corresponding replacements at the 2- and 6-positions, allows for facile preparation of material labeled at C-8 only. Although isotopic contamination at C-2 does occur to a small degree in some cases, any reaction rates obtained from such samples are not invalidated as the exchange velocity for a tritium atom at the 8-position is dramatically different from that at C-2.⁴³ With adenine, for example, the 2-³H exchange is some 2000 times slower than that for the 8-³H-labeled purine. Similar considerations apply to deuterated derivatives also.

1. Reaction Rates

Using the deuterium-labeled purine, the disappearance of the isotope at C-8 when in the presence of water is monitored by noting the corresponding increase in height (or area) of the signal due to the 8-proton.^{44,45,48}

⁴² E. Kriek, *Cancer Res.* **32**, 2042 (1972).

⁴³ J. A. Elvidge, J. R. Jones, and C. O'Brien, *J. Chem. Soc., Chem. Commun.*, 394 (1971).

⁴⁴ J. A. Elvidge, J. R. Jones, C. O'Brien, E. A. Evans, and H. C. Sheppard, *J.C.S. Perkin II*, 1889 (1973).

⁴⁵ J. A. Elvidge, J. R. Jones, C. O'Brien, E. A. Evans, and H. C. Sheppard, *J.C.S. Perkin II*, 2138 (1973).

⁴⁶ M. Maeda, M. Saneyoshi, and Y. Kawazoe, *Chem. Pharm. Bull.* **19**, 1641 (1971).

⁴⁷ M. Tomasz, J. Olsen, and C. M. Mercado, *Biochemistry* **11**, 1235 (1972).

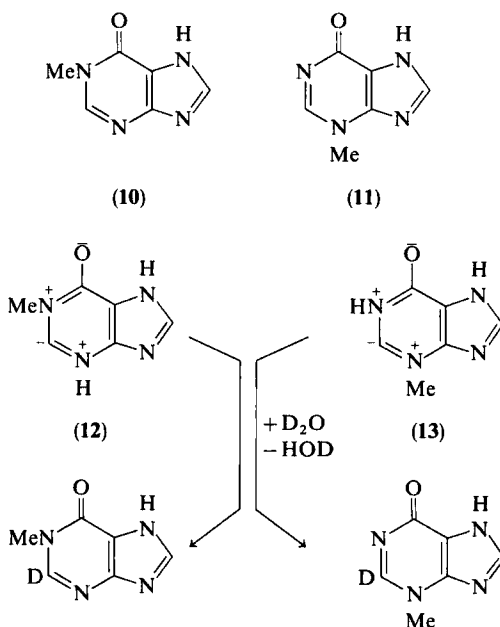
⁴⁸ J. A. Elvidge, J. R. Jones, C. O'Brien, E. A. Evans, and H. C. Sheppard, *J.C.S. Perkin II*, 174 (1974).

⁴⁹ J. L. Wong and J. H. Keck, *J. Chem. Soc., Chem. Commun.*, 125 (1975).

⁵⁰ D. Lichtenberg and F. Bergmann, *J.C.S. Perkin I*, 789 (1973).

⁵¹ J. Szydłowski and M. Jelinska, *Radiochem. Radioanal. Lett.* **19**, 355 (1974).

With the tritiated purines only tritium exchange in water has been extensively investigated.⁴⁴ Exchange rates for simple purines are given in Table I. The reaction velocities can be influenced by a variety of factors, both endogenous and exogenous. Substituents located on pyrimidine ring-carbon atoms, whether electron-attracting or -withdrawing, have little effect (see Table I), but alkylation of ring nitrogen atoms can profoundly perturb the electron density at C-8. For example, whereas hypoxanthine methylated at N-1 (**10**) shows only a slightly enhanced exchange rate of deuterium at C-8, the reverse effect, of quite high order, is noted with the N-3 methylated analog (**11**).⁴⁹



The results are explained in terms of the respective increase and decrease in basicity experienced by the N-7 atom in the above derivatives compared with that of the corresponding atom in the parent purine. The decrease in activity of the 8-hydrogen in extreme cases may be so large as to render the 2-carbon the more electrophilic of the two, and thus preferentially exchanged. To explain the reversal in activity of 8-H and 2-H, zwitterionic forms (**12** and **13**) have been postulated in which the nitrogen atom adjacent to the carbon bearing the exchangeable hydrogen is the one associated with the positive charge.^{49,52} Thus, charges at either N-1 or N-3 would lead to enhanced exchange at C-2 in these derivatives.

⁵² A. D. Broom and G. H. Milne, *J. Heterocycl. Chem.* **12**, 171 (1975).

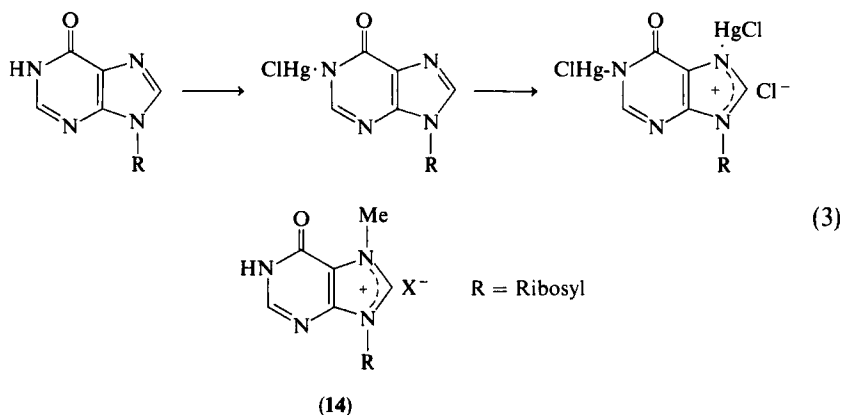
TABLE I
 RATE-pH DATA FOR 8-³H-LABELED PURINES

$10^6 k_{\text{obs}} \text{ sec}^{-1}$						
pH at 85°	Purine ^a	9-Isopropyl- purine ^a	Adenine ^b	Guanine ^c	Hypoxanthine ^c	9-Methyl- hypoxanthine ^c
2.05 ^d	—	—	2.26	0.74	—	3.14
2.15 ^d	13.1	34.5	—	—	1.80	—
2.31	16.9	43.5	—	—	—	—
2.51 ^d	20.6	54.9	—	1.86	—	—
2.55	—	—	4.50	—	—	—
2.75 ^d	23.4	70.0	—	2.71	—	—
2.83	—	—	—	2.65	—	—
3.00	—	—	—	3.15	—	—
3.12	26.6	82.5	11.8	—	2.88	5.50
3.50	—	—	—	4.02	—	—
3.60	—	—	18.5	—	—	—
3.70	—	—	20.4	—	—	—
3.90	—	—	24.1	—	—	—
4.10 ^d	—	—	26.4	—	2.95	—
4.65	—	—	32.4	—	—	—
5.45	31.8	—	—	—	—	—
6.25	32.0	104	33.0	4.45	2.82	5.70
7.20	—	—	—	—	8.25	18.1
7.75	—	—	—	—	—	37.8
8.02	—	—	—	—	—	45.5
8.38	—	—	29.2	7.70	—	—
8.77	—	—	—	8.90	—	—
9.06	—	—	20.4	18.4	—	—
9.30	—	—	8.10	22.2	—	—
9.42	—	—	4.00	—	—	—
9.50 ^d	2.71	—	—	—	11.7	—
10.02	—	—	—	26.8	—	—
10.10	—	—	3.06	—	—	—
10.20	—	—	—	—	10.5	84.5
10.40	—	—	2.02	—	—	—
10.50	—	256	—	22.6	10.6	91.0
11.20	—	735	—	—	6.86	93.4

^a Data from Elvidge *et al.*⁴⁴^b Data from Elvidge *et al.*⁴⁵^c Data from Elvidge *et al.*⁴⁸^d Values within range ± 0.03 .

Any factor that induces a more positive character in the imidazole ring will facilitate exchange at C-8. This is seen in the effect produced by the presence of the weakly electron-withdrawing ribosyl group, the exchange rate for adenosine being twice that of adenine itself.⁴³ Where, however, a

formally charged structure is involved, as in the case of quaternary salts, the rate increases dramatically and the 8-H signal in the NMR spectrum is displaced strongly downfield.⁵²⁻⁵⁴ In the presence of D₂O the exchange may be too rapid to be observed spectroscopically.⁵³ A further related example is evident when methylmercury(II) ions and inosine are allowed to react. When the ratio of reactants becomes greater than 1:1 in favor of the mercury derivative, the signal due to 8-H starts to disappear if D₂O is present. By analogy with the alkylation pattern for inosine, this result would suggest an initial complex formation involving N-1 being followed by secondary reaction at N-7 in the other ring, leading to a quaternary structure with a highly labile 8-H [Eq. (3)].⁵⁵ In this context it should be noted that



with the structurally related 7-methylinosine (14), exchange in D₂O of 8-H is too rapid to be measured.⁵⁵

2. Effect of pH

Purine itself and other purines not substituted at N-7 or N-9 show a similar rate curve with change in pH, a bell-shaped plot being obtained with low rates at high (>12) and low (<2) pH values (Fig. 1).⁴⁴ Between this pH range the monoprotinated, neutral, and anionic forms are encompassed, the midpoints of the ascending and descending parts of the curve corresponding to the dissociation constants for the cation and neutral molecule, respectively. At high pH values the predominance of the anionic

⁵³ P. O. P. Ts'o, N. S. Kondo, R. K. Robins, and A. D. Broom, *J. Am. Chem. Soc.* **91**, 5625 (1969).

⁵⁴ R. Roe, J. S. Paul, and P. O. Montgomery, *J. Heterocycl. Chem.* **10**, 849 (1973).

⁵⁵ S. Mansy and R. S. Tobias, *J. Chem. Soc., Chem. Commun.*, 957 (1974).

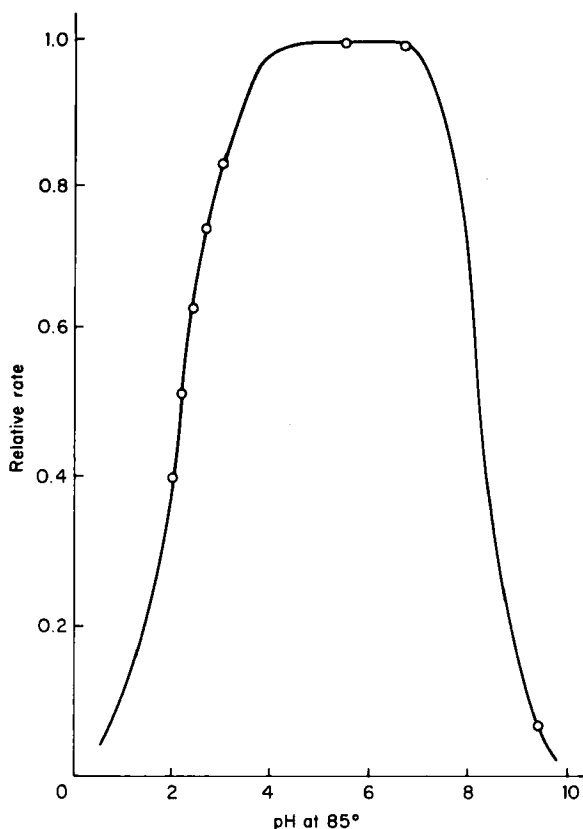


FIG. 1. Rate-pH profile for proton exchange with $[8\text{-}^3\text{H}]\text{purine}$ at 85° . (From Elvidge *et al.*⁴⁴)

species, with consequent localization of negative charge in the five-membered ring, inhibits further exchange of 8-H.

Where an imidazole nitrogen is substituted, as in 7- or 9-alkyl purines,⁴⁴ the exchange rates for low and intermediate pH values are similar to those for purine. As pH increases, however, the rate of hydrogen abstraction does not decline, but accelerates dramatically (Fig. 2). Possible factors for this anomalous behavior are discussed in Section III,A,3.

3. Mechanism of Exchange

The fact that most purines undergo exchange of the 8-hydrogen at low to neutral pH values but, depending on whether or not they can form the anion, show a respective cessation or acceleration of the exchange velocity

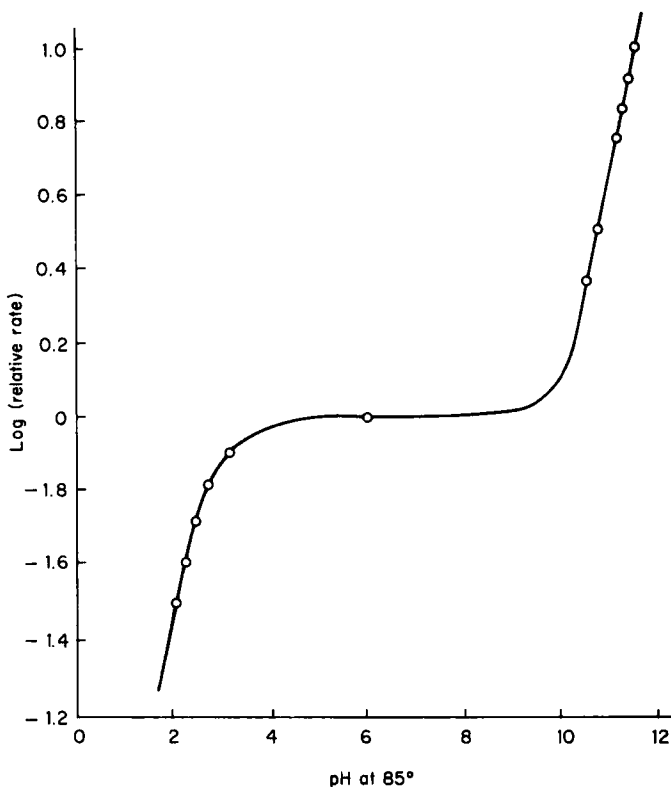
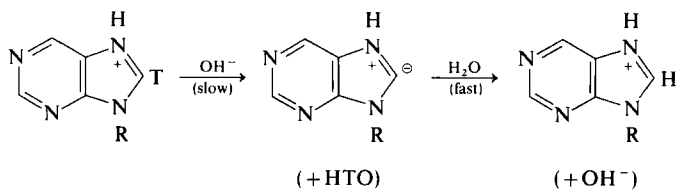


FIG. 2. Rate-pH profile for proton exchange with 9-isopropyl-[8- ^3H]purine at 85°. (From Elvidge *et al.*⁴⁴)

at high pH values points toward more than one mechanistic pathway being followed.

Under low-pH conditions the behavior observed parallels that shown by imidazoles undergoing exchange of the hydrogen at C-2, this position being equivalent to C-8 in purines. As a plausible mechanism has been formulated for the imidazole exchange,⁵⁶ an adaptation of this has found acceptance as a rationale for the purine mechanism also.^{44,47} A first-stage protonation on nitrogen is envisaged with subsequent abstraction of hydrogen by hydroxyl ion from C-8 of the resulting conjugate acid. This slow, rate-determining step is followed by a fast step in which the ylid is protonated by means of the water molecules (Scheme 1). It has been pointed out that purines are usually protonated first on pyrimidine, not imidazole, ring

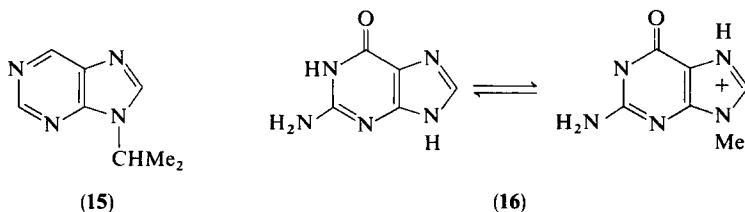
⁵⁶ J. D. Vaughan, Z. Mughrabi, and E. C. Wu, *J. Org. Chem.* **35**, 1141 (1970).



SCHEME 1

nitrogen atoms. This objection has been countered by the proposition that even if only a minority of the purine molecules are imidazole-protonated in equilibrium with the other protonated species the reaction could succeed.⁴⁷ Indirect support for this proposal is given by the fact that the hydrogen abstraction step is slow and is the rate-determining stage. Additional to this is that molecular orbital calculations⁵⁶ point to the ylid form as being the most likely intermediate in the replacement process.

Another mechanism has to be sought to explain the sudden and rapid increase in reaction velocity that is seen with non-anion-forming purines at high pH values. Thus, the rate for detritiation of 9-isopropylpurine (**15**) at pH 11.5 is eleven times greater than the rate at pH 6.25.⁴⁴ The overall findings from studies of this phenomenon indicate that it is the neutral molecule that suffers hydrogen abstraction by means of the hydroxyl ion present. The suggestion that adoption of a zwitterionic form by the neutral



molecule, as for example **16** by 9-alkylguanine, would best explain ease of hydrogen removal has had some support,^{47,50} but, although attractive, it does not explain the high rates found in some purines not capable of zwitterion formation, e.g., 9-isopropylpurine (**15**).

B. RADICAL REACTIONS

Purine and purines having no substituent at C-6 when exposed to radicals are converted into the appropriate 6-substituted purine. The preference for reaction at the 6-position, rather than the 8-position as might be expected

with electrophilic type agents, is supported by free valence calculations.⁵⁷ These data, which reflect the likelihood of positions to undergo radical attack, show that while the 6-position is the most favored only a small difference exists in reactivity between the 6- and 8-positions. This is illustrated by the isolation of some 6,8-disubstituted purines in addition to the main product.

Most of the purines investigated have had an atom or group at the 6-position so that the major products arise from radical attack at C-8 with further reaction at C-2 occasionally occurring.

1. *Radical Propagation*

Diverse sources of organic radicals exist that require equally varied means for their propagation. Radiation provides a convenient method for generating radicals in solution, the radiation may be derived from ⁶⁰Co (γ-rays), X-irradiation, or short (> 260 nm) or long (> 290 nm) wavelength ultraviolet light. In the last case (> 290 nm) photosensitizers, usually ketones or aliphatic peroxides, if incorporated are found to increase yields of products. Sunlight or visible light (> 370 nm) also find occasional use in this work. Chemical means are largely based on Fenton-type reagents, in which an oxidant is combined with hydrated ferrous sulfate. The radical precursor in such cases may be separate from the oxidizing agent or incorporated with it as, for example, in the methyl radical sources *t*-butylperacetate or *t*-butylhydroperoxide. Corresponding radical moieties can be obtained from hydrocarbons, alcohols, alkyl halides, amines, and ethers with these mixtures. In the same way acylating groups can be derived from aldehydes and amides.

2. *Hydrogen and Hydroxyl Groups*

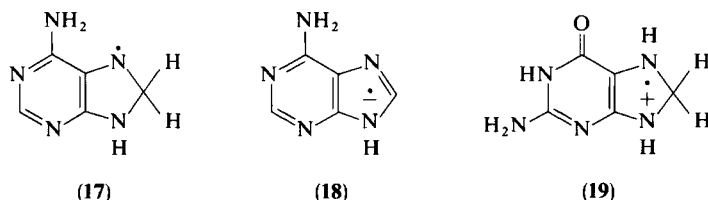
The fate of purines, either when subjected to bombardment by atomic hydrogen⁵⁸ in the microcrystalline state or to X-irradiation⁵⁹ in alkaline solution, has been studied by ESR techniques. Adenine and guanine give rise to hydrogen adduct radicals of type **17** with atomic hydrogen, possibly the same derivatives are obtained from X-irradiation in which electron capture gives first the anion radical intermediate (**18**), this being followed by hydrogen addition using the solvent molecules as hydrogen donors.⁵⁹

As large single crystals provide more detailed structural information than powder samples in ESR work, some use has been made of purine salts. In

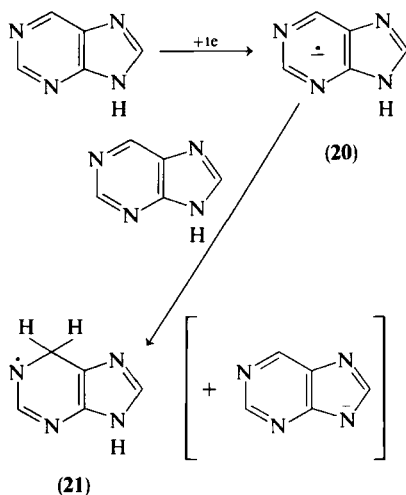
⁵⁷ B. Pullman and A. Pullman, *Proc. Natl. Acad. Sci. U.S.A.* **45**, 136 (1959).

⁵⁸ J. N. Herak and W. Gordy, *Proc. Natl. Acad. Sci. U.S.A.* **54**, 1287 (1965).

⁵⁹ A. Van De Vorst and Y. Lion, *Jerusalem Symp. Purines* **4**, 362 (1972).



the case of guanine hydrochloride, as the dihydrated form, the radical adduct is in the protonated form (19),⁶⁰ when exposed to γ -irradiation. The presence of intermediate radical forms of type 18 has been demonstrated by polarography of purines in aprotic solvents, e.g., acetonitrile, dimethylformamide.^{61,62} In contrast to reduction in aqueous solvents, this procedure exhibits only a 1e reduction stage and the unstable radical ion (20) initially formed stabilizes itself as the radical (21) by proton capture from a neighboring purine molecule (Scheme 2). Subsequently, radical interaction may



SCHEME 2

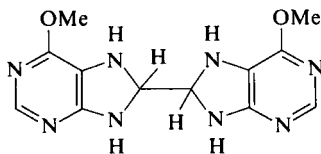
ensue, giving a 6,6'- or 8,8'-linked dimer (e.g., 22), the linking mode depending on whether a 6-unsubstituted (purine) or 6-substituted purine (adenine, 6-methylpurine, 6-methylaminopurine, or 6-methoxypurine) is employed. After γ -irradiation of an aqueous solution of adenine, 6-amino-8-hydroxy-8,9-dihydropurine (23) was identified as a product.⁶³ This is of interest in

⁶⁰ C. Alexander and W. Gordy, *Proc. Natl. Acad. Sci. U.S.A.* **58**, 1279 (1967).

⁶¹ K. S. V. Santhanem and P. J. Elving, *J. Am. Chem. Soc.* **96**, 1653 (1974).

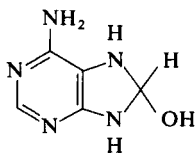
⁶² T. Yao and S. Musha, *Bull. Chem. Soc. Jpn.* **47**, 2650 (1974).

⁶³ J. J. Van Hemmens and J. F. Bleichrodt, *Radiat. Res.* **46**, 444 (1971).

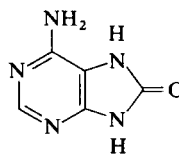


(22)

that it may represent the intermediate stage in the formation of 8-hydroxy-adenine (24) by the action of hydroxyl radicals on adenine.^{64,65}



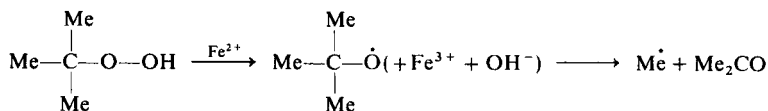
(23)



(24)

3. Alkyl Groups

The 8-methyl homolog of a number of 6-substituted purines have been obtained using *t*-butyl hydroperoxide in the presence of ferrous sulfate acidified with sulfuric acid (Scheme 3).^{66,67} With adenine and hypoxanthine,



SCHEME 3

some of the 2-mono- and 2,8-dimethylated derivatives were isolated also (Scheme 4). The corresponding 8-methyl analogs are formed from adenosine and guanosine when treated with a diacetylperoxide-ferrous sulfate mixture,⁶⁸ the methyl radicals arising in this instance by degradation of the acetoxy radical formed from the diacetyl peroxide.

Ferrous ion-catalyzed degradation of *t*-butyl peracetate can be replaced by either photochemical or thermolytic breakdown procedures, of which the former, using light of >300 nm, is a better means of methyl radical

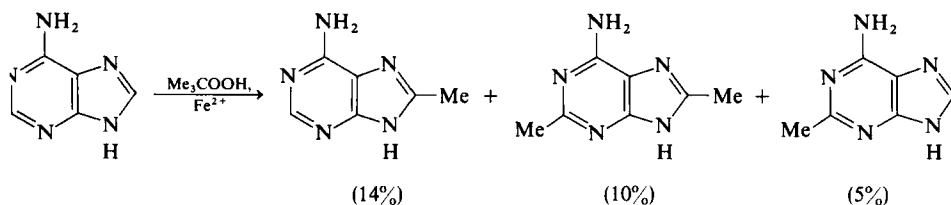
⁶⁴ J. J. Conley, *Nature (London)* **197**, 555 (1963); E. Fahr, *Angew. Chem. Int. Ed. Engl.* **8**, 578 (1969).

⁶⁵ N. Mariaggi and R. Teoule, *C. R. Acad. Sci., Ser. C* **279**, 1005 (1974).

⁶⁶ M. Maeda, K. Nushi, and Y. Kawazoe, *Tetrahedron* **30**, 2677 (1974).

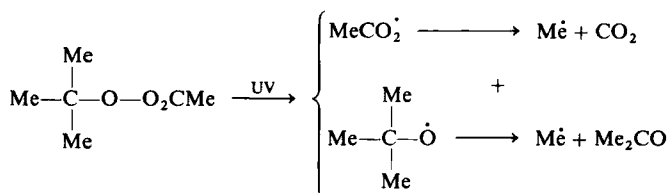
⁶⁷ Y. Kawazoe, M. Maeda, and K. Nushi, *Chem. Pharm. Bull.* **20**, 1341 (1972).

⁶⁸ M. Araki, M. Maeda, and Y. Kawazoe, *Tetrahedron* **32**, 337 (1976).



SCHEME 4

production. Using a 1200 W lamp source *t*-butyl peracetate methylates caffeine 28 times faster (Scheme 5) than *t*-butyl hydroperoxide.⁶⁹ Benzylation



SCHEME 5

is also achieved by radical means in the preparation of an 8-benzylguanosine derivative by treating the guanosine with toluene in the presence of ammonium persulfate and acidified ferrous sulfate.⁷⁰ In a further example, UV irradiation (> 250 nm or > 290 nm) of an aqueous solution of theophylline (anionic form) containing benzyl bromide gave 8-benzyltheophylline in addition to the expected 7-benzyl isomer.⁷¹ Alkyl radicals may also arise as secondary radicals from *inter alia* alcohol or amine precursors. These reactions are noted in the appropriate sections below.

4. Hydroxyalkyl Groups

Initial studies were made with purine in methanol exposed to shortwave (> 250 nm) UV light,^{72,73} the photo product being derived from addition of the alcohol across the 1,6-double bond. This work was later extended to purine nucleoside (nebularine)⁷⁴ and 2-aminopurine⁷⁵ and the use of other

⁶⁹ M. F. Zady and J. L. Wong, *J. Am. Chem. Soc.* **99**, 5096 (1977).

⁷⁰ L. F. Christensen, R. B. Meyer, J. P. Miller, L. N. Simon, and R. K. Robins, *Biochemistry* **14**, 1490 (1975).

⁷¹ K. Bhushan and J. H. Lister, *Aust. J. Chem.* **29**, 891 (1976).

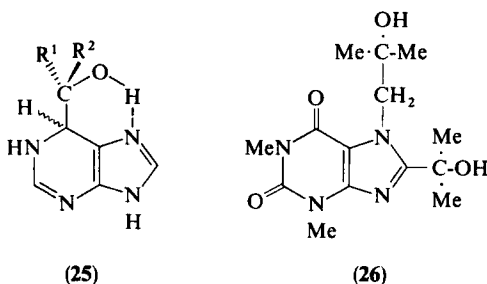
⁷² H. Linschitz and J. S. Connolly, *J. Am. Chem. Soc.* **90**, 2979 (1968).

⁷³ J. S. Connolly and H. Linschitz, *Photochem. Photobiol.* **7**, 791 (1968).

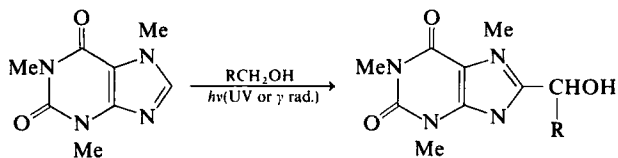
⁷⁴ B. Evans and R. Wolfendon, *J. Am. Chem. Soc.* **92**, 4751 (1970).

⁷⁵ H. Steinmaus, I. Rosenthal, and D. Elad, *J. Org. Chem.* **36**, 3594 (1971).

alcohols. In the case of the ethanol adduct, two products were obtained. NMR and infrared (IR) data indicated that these were diastereomeric forms for which the preferred conformations about the purine(C-6)-ethanol(C α) bond (**25**: R¹ = Me; R² = H) and (**25**: R¹ = H; R² = Me) have been proposed.⁷³ Possible enhancement of this effect by intramolecular hydrogen bonding between the hydroxyl group and N-7 (or, less likely, N-1) was also suggested.⁷³



The major effort has been directed toward radical attack at C-8. Adenine, hypoxanthine, 6-ethoxypurine, guanine, and caffeine give the corresponding 8-hydroxyalkyl derivative when a solution in the alcohol is subjected to either UV light or γ -irradiation (Scheme 6). In all cases the alcohol radical



is formed through homolytic fission of hydrogen from the same carbon to which the hydroxyl group is attached. As a generalization better results are found using longer wavelength (>290 nm) UV light in the presence of sensitizers, of which acetone,⁷⁵⁻⁷⁷ di-*t*-butylperoxide⁷⁸ or dicumylperoxide⁷⁸ have been the most widely employed. In the absence of UV light Fenton's reagent (ferrous sulfate-hydrogen peroxide) is capable of converting guanine in methanol into the 8-hydroxymethyl analog.⁶⁶

In the 8-hydroxyalkylpurine series, no diastereomeric forms analogous to those found in the 6-hydroxyethylpurines appear to have been found.

⁷⁶ D. Elad, I. Rosenthal, and H. Steinmaus, *J. Chem. Soc., Chem. Commun.*, 305 (1969).

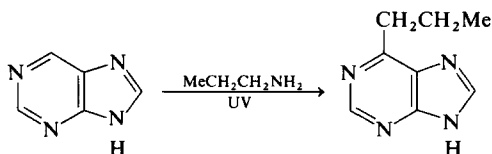
⁷⁷ H. Steinmaus, I. Rosenthal, and D. Elad, *J. Am. Chem. Soc.* **91**, 4921 (1969).

⁷⁸ J. Salomon and D. Elad, *J. Org. Chem.* **38**, 3420 (1973).

Side effects in some reactions give rise to 8-alkylpurines⁷⁸ also, although the stage at which dehydroxylation occurs is not clear. Some extraneous radical attack at *N*-methyl groups may also take place, illustrated by the isolation of the derivative **26** following caffeine–isopropanol interaction.⁷⁸

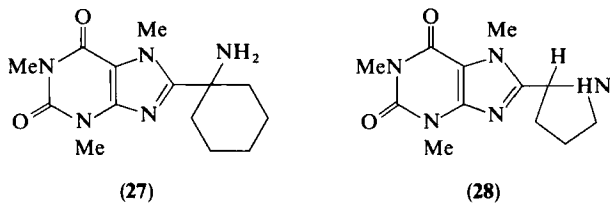
5. Aminoalkyl Groups

Corresponding reactions to those noted above with alcohols are found to occur with amines, the radical produced being derived by hydrogen abstraction from the carbon linked to the heteroatom. Radical generation can be effected with γ -irradiation or UV light (>250 nm or >290 nm) using either liquid amines or aqueous solutions. The tendency to lose the heteroatom from the radical moiety is more pronounced than with the alcohol derivatives. The extreme case is found with 6-unsubstituted purines, in which no 6-aminoalkylpurine is obtained; concomitant deamination occurs giving the 6-alkylpurine⁷⁹ as product (Scheme 7).



SCHEME 7

Adenine and caffeine give mixtures of the 8-aminoalkyl- and 8-alkylpurines,^{80–82} and the diversity of amines applicable is seen in the formation of derivatives **27** and **28** with cyclohexylamine and pyrrolidine.⁸¹



The mechanism of the deamination has not been investigated but is more pronounced with a secondary ($\text{—CH}_2\text{NH}_2$) rather than a tertiary (>CHNH_2) α -carbon in the amine. Although the amino group could be

⁷⁹ N. C. Yang, L. S. Gorelic, and B. Kim, *Photochem. Photobiol.* **13**, 275 (1971).

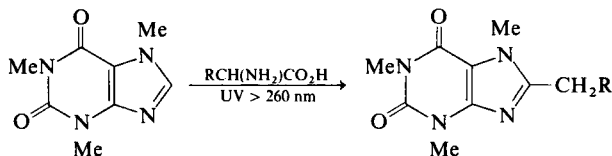
⁸⁰ J. Salomon and D. Elad, *Photochem. Photobiol.* **19**, 21 (1974).

⁸¹ D. Elad and J. Salomon, *Tetrahedron Lett.*, 4783 (1971).

⁸² A. Stanukas, I. Rosenthal, and J. N. Pitts, *Tetrahedron Lett.*, 4779 (1971).

removed with equal facility at either the radical or adduct stage, one pointer toward the latter being the case is that on further photolysis (>260 nm) in methanol an 8-aminoalkylpurine is converted into the 8-alkyl analog.⁸⁰

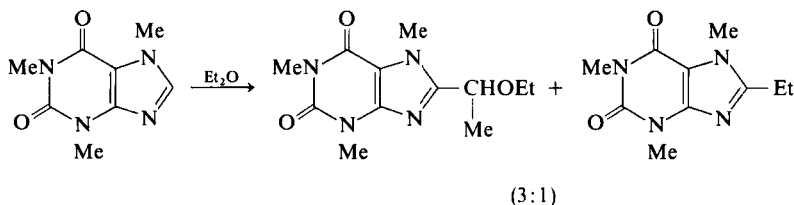
When α -amino acids are employed not only deamination but decarboxylation occurs affording the 8-alkylpurine (Scheme 8).⁸³



SCHEME 8

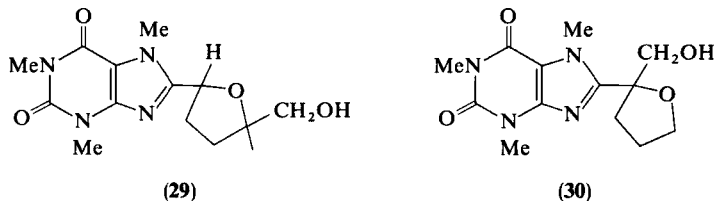
6. Alkoxyalkyl Groups

Caffeine and diethyl ether, under irradiation in the presence of acetophenone, give a 3:1 mixture of 8-(1-ethoxyethyl)- and 8-ethyl-caffeine (Scheme 9).⁸⁴ Loss of the alkoxy group therefore parallels removal of the



SCHEME 9

heteroatom-containing group in the alcohol (Section III,B,4) and amine (Section III,B,5) adducts. Cyclic ethers, including tetrahydrofuran, tetrahydropyran, dioxane, and dioxolane derivatives, have been successfully employed by these and other workers.⁸⁵ When tetrahydrofuryl alcohol and



⁸³ D. Elad and I. Rosenthal, *J. Chem. Soc., Chem. Commun.*, 905 (1969).

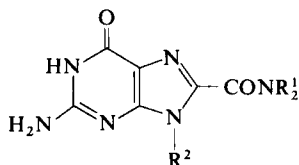
⁸⁴ S. Jerumanis and A. Martel, *Can. J. Chem.* **48**, 1716 (1970).

⁸⁵ D. Leonov and D. Elad, *J. Org. Chem.* **39**, 1470 (1974).

caffeine interacted, two derivatives resulted (**29** and **30**) in 2.5:1 ratio. A noteworthy point is that both isomers are formed through a radical arising from homolysis of the C—H bond α to the ether oxygen rather than that α to the alcohol group. Analogous derivatives of adenine and guanine have been similarly prepared.⁸⁵

7. Acyl Groups

Derivatives containing acyl moieties, for example aldehydes, undergo homolytic fission affording acyl radicals. In this way, using acetaldehyde, butyraldehyde, 2-methylpropaldehyde, and benzaldehyde, and an acidified ferrous sulfate-ammonium persulfate combination as initiator, the respective 8-acetyl, -butyryl, -isobutyryl, and -benzoyl derivatives of guanosine have been formed.⁷⁰ Although inosine gave analogous products with aldehydes, no reaction was reported to take place with adenosine.⁷⁰ The scope of acylation can be extended to include carbamoyl derivatives by using amides as radical sources. With formamide and *N,N*-dimethylformamide the corresponding 8-carbamoyl (**31a**)⁷⁰ and 8-(*N,N*-dimethylcarbamoyl)purine (**31b**)⁶⁶ have resulted with guanosine.



(31)

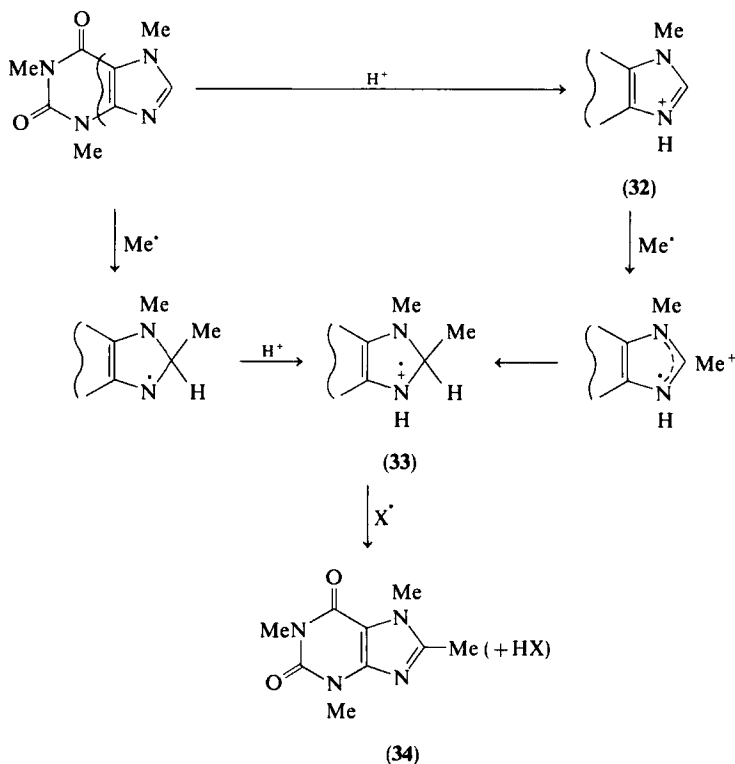
a: $R^1 = H$; $R^2 = \text{ribosyl}$
 b: $R^1 = \text{Me}$; $R^2 = \text{ribosyl}$

8. Mechanism of Substitution

With photochemical or γ -irradiation experiments, initially neutral conditions obtain as a general rule. After exposure to short wavelength (> 250 nm) light the purine molecule is raised to an excited state by absorption and can abstract hydrogen from the radical precursor molecule. The resulting radical is thus available for reaction with a neighboring purine molecule. With the longer wavelength (> 290 nm) light or γ -irradiation, using a sensitizer, the latter is now the major light absorber and following excitation is degraded to a radical form which, by interaction with the required radical source (alcohol, amine, etc.) converts it to the active species. This new radical is now available for attack on a ground-state purine molecule. As noted earlier (Section III,A,3) radical attack on the purine is followed by a protonation

step and the resulting 8,9-dihydropurine being highly unstable⁸⁶ would be rapidly oxidized to the purine analog.

A detailed mechanism and kinetic study of methylation at C-8 of caffeine, embracing acid and neutral conditions, has been made.⁶⁹ With *t*-butyl peracetate (BPA) as methyl radical source, the rate constants for caffeine-BPA interactions as functions of temperature, concentration, pH, and solvent and kinetic isotope effects have been determined (Table II).⁶⁹ Activation energies derived from the Arrhenius equation using values in Table II show $\Delta G^\ddagger = 23.5 \text{ kcal mol}^{-1}$ and $\Delta S^\ddagger = -11.7 \text{ cal mol}^{-1} \text{ K}^{-1}$ at 25° and favor an S_EAr type mechanism operating. The negative value obtained for ΔS^\ddagger is a strong indication that under either acid or neutral conditions a σ -complex would be expected as a common intermediate. Scheme 10 illustrates the respective pathways followed under neutral or acid conditions. The rate determining step under the former conditions is protonation following



SCHEME 10

⁸⁶ S. M. Hecht, B. L. Adams, and J. W. Kozarich, *J. Org. Chem.* **41**, 2303 (1976).

TABLE II
RATE CONSTANTS FOR RADICAL C-8
METHYLATION OF CAFFEINE
WITH *t*-BUTYLPERACETATE^a

Reaction	Conditions	$10^5 k / \text{sec}^{-1}$ ^{b,c}
Thermal	58°	None observed
Thermal	65°	0.40 (± 0.01)
Thermal	80°	1.67 (± 0.18)
Thermal	95°	7.61 (± 0.37)
UV light (Pyrex filter)	450 W/25°	1.39 (± 0.02)
UV light (Pyrex filter)	1200 W/25°	6.67 (± 0.36)

^a *tert*-Butylperacetate-caffeine (3:1 *M* ratio) in D₂O-CF₃CO₂D (2:1) solution.

^b *k* was determined by observing (¹H NMR, HPLC) appearance of 8-methylcaffeine.

^c Data from Zady and Wong.⁶⁹

methylation of the purine, while at lower pH the controlling factor is methylation of the conjugate acid (32). In either situation the net effect is formation of the σ -complex 33, which then suffers loss of hydrogen, possibly abstracted by the acetoxyl radical, to give either the aromatized form (34) or the protonated analog, according to the conditions prevailing. A comparison of rate constants for various purines (Table III) shows all values to lie within a narrow range and demonstrates that the effect of substituent groups on the kinetics of radical alkylation is minimal.

C. IONIC ALKYLATION

Cited under this heading are various examples of alkylation at the 8-position which take place under conditions that favor participation by ionic rather than radical agents.

In the earliest reaction of this type, with theophylline and crotyl bromide in alkali at ambient temperature, 8-(but-2-enyl)theophylline (35) was obtained as the sole product.⁸⁷ A recent repeat of this preparation gave an identical

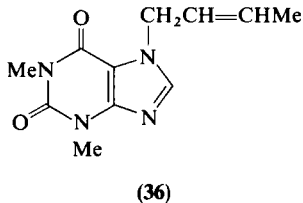
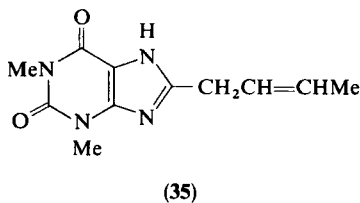


TABLE III
RATE CONSTANTS FOR
C-8 METHYLATION OF
PURINES WITH
t-BUTYLPERACETATE^a

Purine ^b	10 ⁵ <i>k</i> /sec ^{-1 c,d}
Adenine	1.18 (±0.14)
Adenosine	1.87 (±0.06)
Guanine	3.85 (±0.06)
Guanosine	4.30 (±0.26)
Hypoxanthine	4.02 (±0.20)
Inosine	3.92 (±0.20)

^a Methyl radicals generated photochemically using 1200 W Hg lamp equipped with Pyrex filter.

^b In 2:1 D₂O–CF₃CO₂ D solution.

^c *k* was derived from HPLC determinations.

^d Data derived from Zady and Wong.⁶⁹

result, none of the expected 7-alkylated isomer (**36**) being detected.⁷¹ The anionic form of theophylline also figured in a benzylation attempt from which a mixture of the 7- and 8-benzylpurines was claimed to be isolated.⁸⁸ A reexamination of the reaction (aqueous solution at 100°) gave not only the expected 7-benzyltheophylline, but also the 8-benzyl- and 7,8-dibenzyl analogs.⁷¹ It should be pointed out that under the experimental conditions thermal production of benzyl radicals cannot be excluded. Even less clear-cut as to ionic character is the result of treating 2-methylthiopurine with diazomethane in ether. In addition, to 9-methyl-2-methylthiopurine a further product, characterized as *N*-8-dimethyl-2-methylthiopurine, was isolated.⁸⁹ In view of the known *C*-methylating property of diazomethane, this result is not unexpected.⁹⁰ A more recent investigation of this reaction gave three products, identified as the 9-methyl, 7,8-dimethyl, and 8,9-dimethyl homologs of 2-methylthiopurine.⁹¹ While formation of the dimethylated purines can be explained by initial addition of the diazomethane across the 7,8- and

⁸⁷ J. Donat and E. Carstens, *Chem. Ber.* **92**, 1500 (1959).

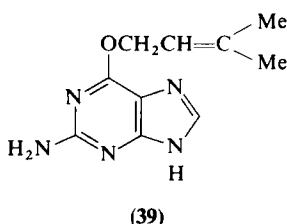
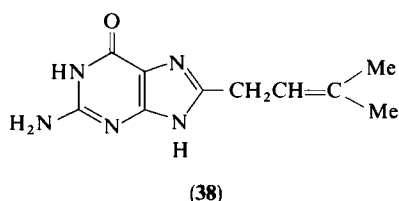
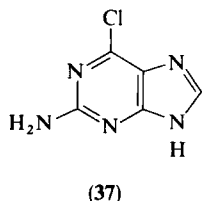
⁸⁸ G. Serchi, L. Sancio, and G. Bichi, *Farmaco, Ed. Sci.* **10**, 733 (1955).

⁸⁹ D. J. Brown and P. W. Ford, *J. Chem. Soc. C*, 2620 (1969).

⁹⁰ R. Gompper, *Adv. Heterocycl. Chem.* **2**, 245 (1963).

⁹¹ J. H. Lister, unpublished work (1978).

8,9-double bonds of the respective 9H and 7H protomeric forms, the possibility of radical attack cannot be discounted with this reagent. An apparently clear-cut example of the facilitation of C-8 electrophilic attack due to the electronegative character of the imidazole moiety in the purine anion is demonstrated in the attempted formation of 2-amino-6-alkoxypurines from the 2-amino-6-chloro analogs.⁹² From the reaction involving the sodio derivative of 3-methylbut-2-enol and 2-amino-6-chloropurine (**37**) in dioxane a good yield (74%) of the 8-alkenylguanine (**38**) was obtained rather than the expected 6-alkenylloxypurine (**39**). The corresponding 8-allyl and 8-crotyl

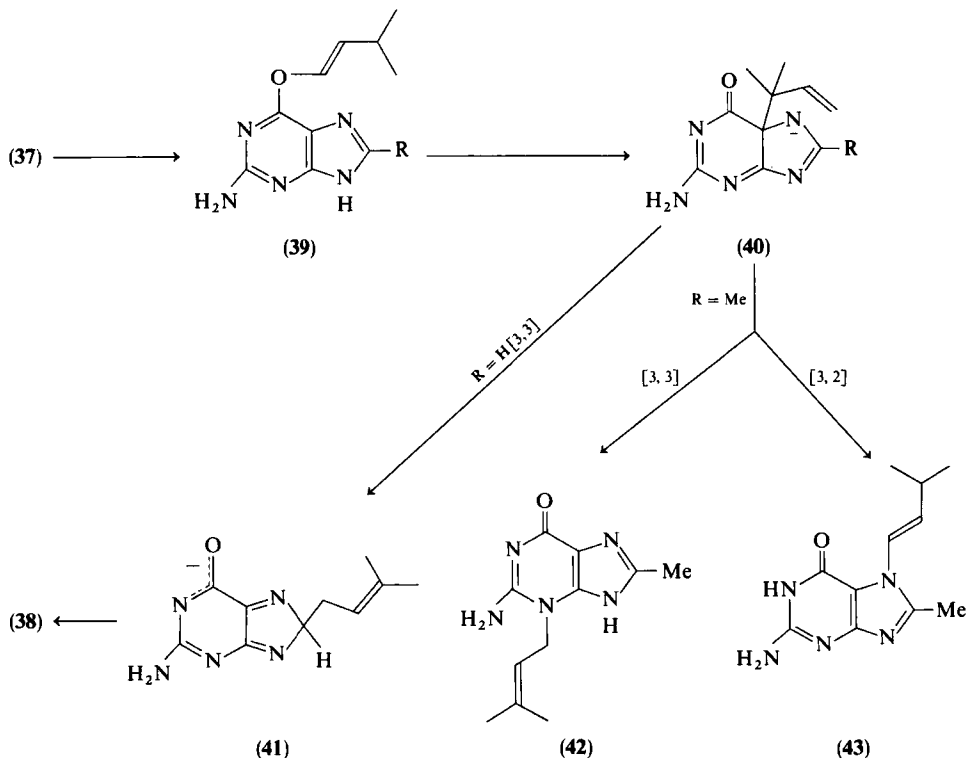


derivatives result using allyl and crotyl alcohols under these conditions. This rearrangement has been studied in detail and found to be intramolecular in type.⁹³ Isolation of the 6-alkoxy intermediate similar to **39** is possible in some cases, and rearrangement to the 8-alkenyl derivative occurs much more rapidly when the anion rather than neutral molecule is used. The mechanism advanced proceeds by way of two consecutive anionic [3,3] sigmatropic shifts, i.e., a combined Claisen–Cope rearrangement, the first of which affords a C-5 linked intermediate (**40**: R = H) and the second, the 8-substituted anion (**41**). Further insight into the nature of the reaction was obtained using the homologous purine in which the 8-position had been blocked by insertion of a methyl group.⁹⁴ With this situation the rearrangement was found to be directed along two other pathways. As with the 8-unsubstituted analog the intermediate resulting from the first [3,3] sigmatropic shift is the C-5 linked purine (**40**: R = Me). Subsequently, by the

⁹² C. R. Frihart and N. J. Leonard, *J. Am. Chem. Soc.* **95**, 7174 (1973).

⁹³ N. J. Leonard and C. R. Frihart, *J. Am. Chem. Soc.* **96**, 5894 (1974).

⁹⁴ B. N. Holmes and N. J. Leonard, *J. Org. Chem.* **41**, 568 (1976).



SCHEME 11

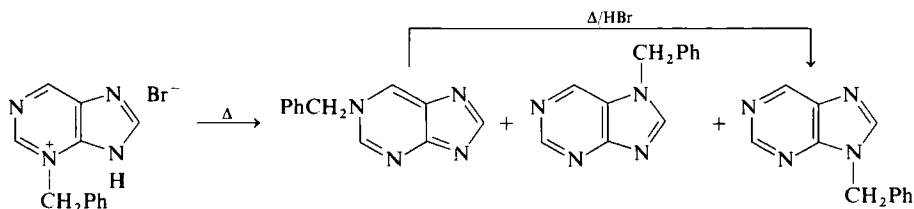
action of a second [3,3] shift the 3-alkenyl isomer (42) could be formed or, alternatively, through the agency of a [3,2] shift the 7-alkenyl derivative (43) would result (Scheme 11).

IV. Group Migration

Translocations studied, mainly those of methyl or benzyl groups, have included movement from ring atom to ring atom, exocyclic atom to ring atom, and ring atom to exocyclic atom; in all cases both donor and recipient atoms are heteroatoms.

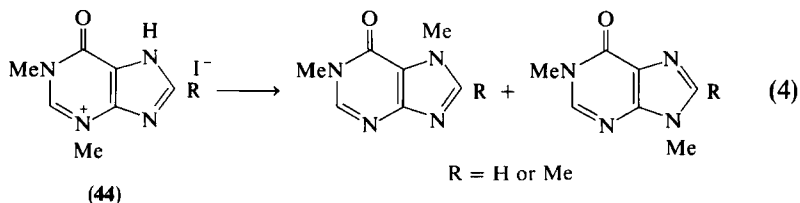
A. BETWEEN RING ATOMS

Heating a solution of 3-benzylpurine hydrobromide (140°/48 hr) in dimethylformamide gives initially a mixture of the 1-, 7-, and 9-benzyl isomers. With further heating interconversion of the 1-benzyl component occurs,

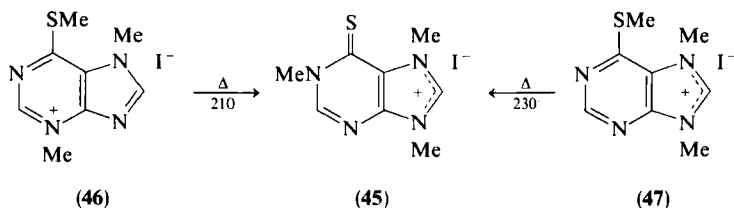


SCHEME 12

leaving a mixture of the 7- and 9-benzyl isomers (Scheme 12).⁹⁵ Under similar conditions the 3-benzyl analogs of adenine and 6-dimethylaminopurine are converted into the 9-benzyl derivatives in significant yields (23–30%).⁹⁵ As isomerizations of the above type fail to occur if hydrogen halides are absent, the mechanism would seem to involve formation of benzyl halides as realkylating agents. Reaction studies using ¹⁴C-labeled derivatives point toward an intermolecular process operating in which the 1- and 3-benzylpurines arise as a result of a kinetically controlled reaction whereas subsequent conversion to the more stable 7- and 9-benzyl isomers is thermodynamically dependent. Migrations of this type also occur with *N*-methylated purines by thermal means. In dimethylformamide the 1,3-dimethylhypoxanthinium iodides (**44**) isomerize to mixtures of the 1,7- and



1,9-dimethyl analogs [Eq. (4)].⁹⁶ A more complex rearrangement of this type is seen when 1,7,9-trimethyl-6-thioxopurinium iodide (**45**) is obtained on fusion of either the 3,7-dimethyl- (**46**) or 7,9-dimethyl-6-methylthiopurinium iodide (**47**) (Scheme 13). Use of deuterated derivatives shows the rearrangement to be nonspecific; *S*- and *N*-methyl groups appear to be

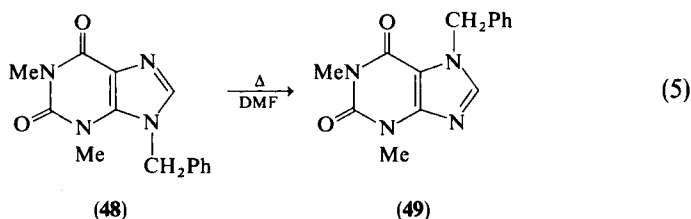


SCHEME 13

⁹⁵ M. Miyaki and B. Shimizu, *Chem. Pharm. Bull.* **18**, 1446 (1970).

⁹⁶ F. Bergmann and M. Rahat, *J.C.S. Perkin I*, 239 (1976).

available for alkylation at various sites. Methyl iodide seems to be the alkylating agent, as fusion of the free bases does not give isomerized products.⁹⁷ Conversion of the 9-benzyltheophylline (48) to the 7-benzyl analog (49) involves benzyl halide as the thermal rearrangement occurs only if hydrogen halide is present [Eq. (5)].⁹⁸ Two examples reported of the conversion of 1,9-dialkylxanthines to 1,3,7-trialkylxanthines utilized similar reaction conditions and a similar or like mechanism appears to be involved.⁹⁹



B. FROM ENDOCYCLIC TO EXOCYCLIC ATOMS

The best-known example is the Dimroth rearrangement of 1-alkyladenines to 6-alkylaminopurines, the parameters and mechanism of which have been established¹⁰⁰ and confirmed by the results of recent mass spectral investigations with deuterated 1-alkyladenine derivatives.^{101,102} The effect of various substituent groups on the rate of rearrangement has been examined.¹⁰³ In addition to studies with 1-alkyladenines the kinetics of the analogous isomerization with 1-alkoxyadenines have been determined and compared.¹⁰⁴

An unrelated reaction mechanistically, but falling under this heading, is the thermal transformation of 3-benzyladenine, under pressure conditions (120°/autoclave), in low yield, into 6-benzylaminopurine. Results of a detailed investigation, involving magnetic resonance and mass spectrometry, point

⁹⁷ Kh. L. Muravich-Aleksandr, A. V. El'tsov, and L. V. Vas'kina, *Zh. Org. Khim.* **11**, 1116 (1975).

⁹⁸ J. H. Lister, *Heterocycles* **6**, 383 (1977).

⁹⁹ F. Yoneda and T. Nagamatsu, *J.C.S. Perkin I*, 1574 (1976).

¹⁰⁰ D. J. Brown, in "Mechanisms of Molecular Migrations" (B. S. Thyagarajan, ed.), Vol. 1, pp. 209-245. Wiley (Interscience), New York, 1968; J. D. Engel, *Biochem. Biophys. Res. Commun.* **64**, 581 (1975).

¹⁰¹ M. H. Wilson and J. A. McCloskey, *J. Org. Chem.* **38**, 2247 (1973).

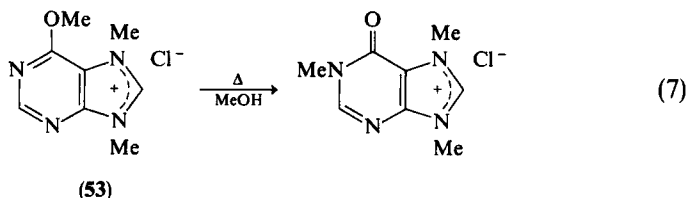
¹⁰² G. Grenner and H. L. Schmidt, *Chem. Ber.* **110**, 373 (1977).

¹⁰³ T. Fujii, T. Itaya, and T. Saito, *Chem. Pharm. Bull.* **23**, 54 (1975).

¹⁰⁴ Y. Itaya, T. Saito, S. Kawakatsu, and T. Fujii, *Chem. Pharm. Bull.* **23**, 2643 (1975).

A so-called "reverse Dimroth" reaction is possible using the differing electron effects produced by methyl and methoxy groups on the ease of rearrangement.¹⁰⁷ In this way a 6-methylaminopurine, after prior conversion to the 1-methoxy derivative (**51**), rearranges readily to the 6-methoxyimino-1-methyl analog (**52**) which on reduction affords the 1-methyladenine (Scheme 14).

Although thermally induced O→N methyl group migrations are well documented for the methoxy analogs of xanthine and uric acid,⁷ the intermolecular isomerization of 6-methoxy-7,9-dimethylpurinium chloride (**53**) to 1,7,9-trimethylhypoxanthinium chloride, in methanol, appears to be the first reported example of a Hilbert-Johnson type reaction involving monoxopurines [Eq. (7)].¹⁰⁸



¹⁰⁷ T. Fujii, F. Tanaka, K. Mohri, and T. Itaya, *Chem. Pharm. Bull.* **22**, 2211 (1974).

¹⁰⁸ J. L. Wong and D. S. Fuchs, *J.C.S. Perkin I*, 1284 (1974).

Advances in Pyrrolizidine Chemistry

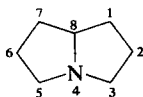
DAVID J. ROBINS

Department of Chemistry, University of Glasgow, Glasgow, Scotland

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I. Introduction

This survey of the chemistry of pyrrolizidine (1) and its derivatives is a continuation of the 1965 review by Kochetkov and Likhoshesterov.¹ For convenience, the same pattern of organization has been adopted. The literature is covered up to 1977. Since the previous review in this series, a comprehensive book on pyrrolizidine alkaloids has appeared² and a series of Annual Reports on alkaloids has been introduced.³ The structures, syntheses, and biological properties of the pyrrolizidine alkaloids are reviewed annually. Other reviews have also been published.^{4,5} Consequently, the emphasis in this review is on material not included in these previous reviews, particularly those syntheses not directed toward naturally occurring pyrrolizidines. The greatest development over the past 15 years has been in the array of synthetic methods available for construction of the pyrrolizidine ring system, and some entirely new concepts have been introduced. Of special interest are the transannular reactions (Section II,G) and the extremely facile and efficient 1,3-dipolar addition methods (Section II,I). In the natural series, an obvious deficiency is of good synthetic routes to the 1,2-dehydropyrrolizidines. [The numbering system used for the pyrrolizidine nucleus in this review is as shown in (1).] As would be expected, great strides have been made over the past few years in spectroscopic analysis of pyrrolizidines, and a new section (IV) is devoted to progress in this area.



(1)

The uses of pyrrolizidine derivatives are many and varied. Pyrrolizidine (1) and simple alkylpyrrolizidines are used as catalysts for the preparation of polymers and resins, particularly polyurethans. They have been utilized also as lubricating oil additives and as hardeners for epoxyresins. A wide

¹ N. K. Kochetkov and A. M. Likhoshesterov, *Adv. Heterocycl. Chem.* **5**, 315 (1965).

² L. B. Bull, C. C. J. Culvenor, and A. T. Dick, "The Pyrrolizidine Alkaloids." North-Holland Publ., Amsterdam, 1968.

³ J. E. Saxton, in "The Alkaloids" (J. E. Saxton, ed.), Specialist Periodical Reports, Vols. 1-5, Ch. 4. Chem. Soc., London, 1971-1975; D. H. G. Grout, in "The Alkaloids" (M. F. Grondon, ed.), Specialist Periodical Reports, Vols. 6 and 7, Ch. 4. Chem. Soc., London, 1976-1977; D. J. Robins, in "The Alkaloids" (M. F. Grondon, ed.), Specialist Periodical Reports, Vol. 8, Ch. 4. Chem. Soc., London, 1978.

⁴ F. L. Warren, in "The Alkaloids" (R. H. F. Manske, ed.), Vol. 12, Ch. 4. Academic Press, New York, 1970.

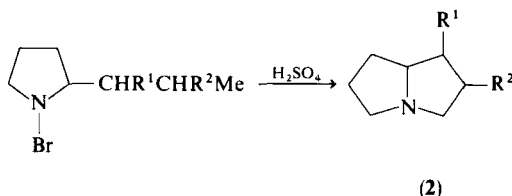
⁵ F. L. Warren, *Fortschr. Chem. Org. Naturst.* **24**, 329 (1966).

range of pharmaceuticals, including anti-inflammatory drugs, has been prepared. Some of the quaternary pyrrolizidine salts are powerful parasitocides. A number of the naturally occurring alkaloids are hepatotoxic and carcinogenic, but some derivatives have potentially useful physiological properties, including anesthetic and antiviral activities.

II. The Synthesis of Pyrrolizidine Derivatives

A. CYCLIZATION OF ALKYL-SUBSTITUTED N-HALOGENOPYRROLIDINES

The cyclization of 2-alkyl-N-bromopyrrolidines to give alkylpyrrolizidines (2) was the first synthetic method used to generate the pyrrolizidine nucleus.¹ This procedure is now mainly of historical interest and has limited practical importance.



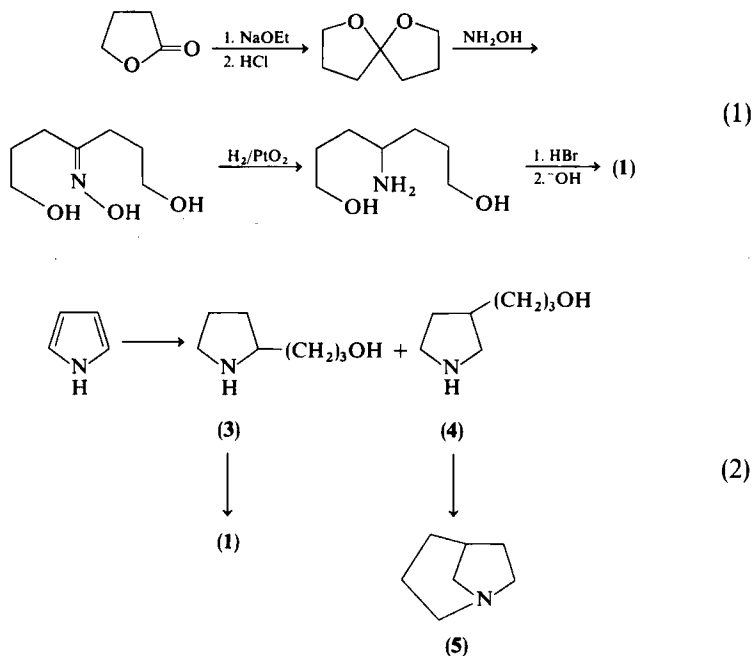
B. CYCLIZATION OF HALIDES AND HALOGENOAMINES AND INTRAMOLECULAR CYCLODEHYDRATION

This group of methods is useful for the preparation of simple alkylpyrrolizidines. Several routes are available to pyrrolizidine (1) from common starting materials. Dedek and Trska⁶ converted γ -butyrolactone into pyrrolizidine in five steps with an overall yield of 12% [Eq. (1)].

A frequently used intermediate in pyrrolizidine syntheses is the hydroxy-alkylpyrrolidine (3). This has been prepared in an improved yield of 40% from pyrrole by Kray and Reinecke,⁷ by Grignard reaction of pyrrol magnesium chloride with trimethylene oxide, followed by catalytic reduction [Eq. (2)]. Some 20% of the product was the isomeric compound (4). Cyclization of the mixture gave the two azabicyclic derivatives (1) and (5). A similar

⁶ V. Dedek and P. Trska, *Collect. Czech. Chem. Commun.* **35**, 651 (1970).

⁷ L. R. Kray and M. G. Reinecke, *J. Org. Chem.* **32**, 225 (1967).



pyrrolidine intermediate was used by Dedek and Barta⁸ in their synthesis of 1-methylpyrrolizidine [Eq. (3)]. The only product of the pyrolysis of the quaternary acetate salt (6) appeared to be (\pm) -heliotridane (7).

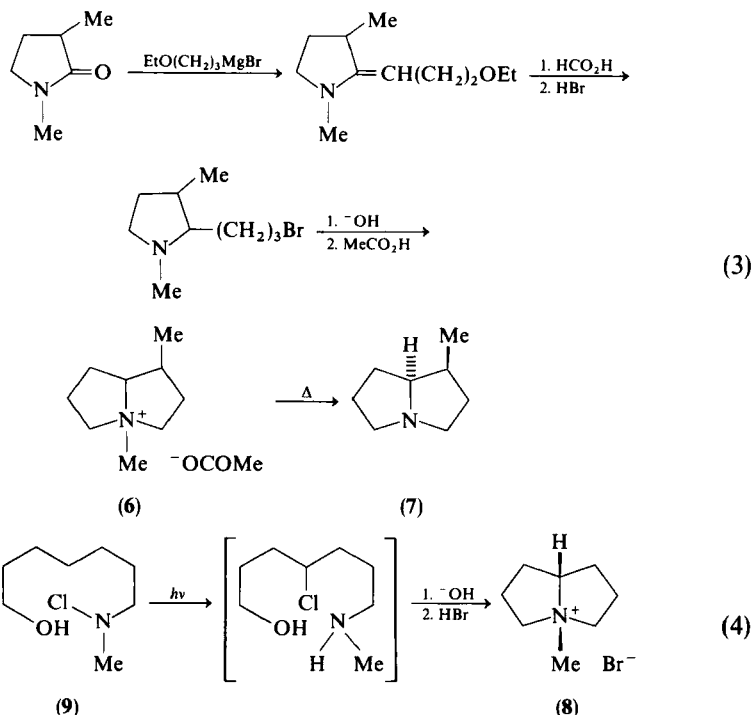
Another synthesis of a quaternary salt (8) was developed by Meyer and Sapianchiay for the purpose of studying the steric course of formation of the pyrrolizidine system.⁹ Photolysis of the *N*-chloroamine (9) in a Hofmann–Loeffler–Freitag reaction [Eq. (4)], gave an intermediate that yielded the pyrrolizidine salt (8) in an intramolecular *N*-alkylation. The product was the *cis*-isomer, reflecting the greater degree of strain in the *trans*-fusion of two five-membered rings.

Russian workers have continued their studies on the production of alkylpyrrolizidines from furan derivatives by catalytic dehydration.¹ The original catalyst used was thorium oxide on alumina, but improved yields were obtained with zirconium oxide on alumina¹⁰ [Eq. (5)]. In the formation of 3-methylpyrrolizidines (10, R = Me), different isomer ratios were observed;

⁸ V. Dedek and M. Barta, *Sb. Vys. Sk. Chem.-Technol. Praze, Org. Technol.* **8**, 89 (1966) [*CA* **67**, 73469 (1967)].

⁹ W. L. Meyer and N. Sapianchiay, *J. Am. Chem. Soc.* **86**, 3343 (1964).

¹⁰ A. A. Ponomarev, I. M. Skvortsov, and A. A. Khorkin, *Zh. Obshch. Khim.* **33**, 2687 (1963) [*CA* **60**, 489 (1964)]; I. M. Skvortsov and G. D. Mikhailov, *Khim. Geterotsikl. Soedin.*, 1127 (1967) [*CA* **69**, 67169 (1968)].



the cis-trans isomer ratio varied from 1:3 to 3:1 depending on the catalyst and temperature.¹¹ A chemical method was recently reported for separating the isomeric 3-methylpyrrolizidines.¹² In a similar manner, varying isomer ratios of other substituted pyrrolizidines were produced using the appropriate starting materials¹³ [Eq. (5)].

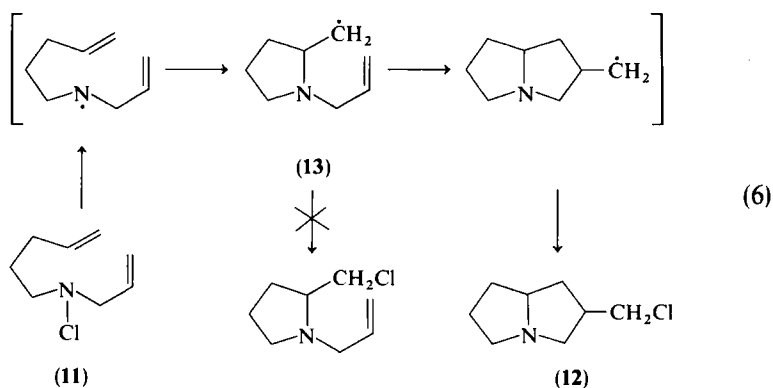
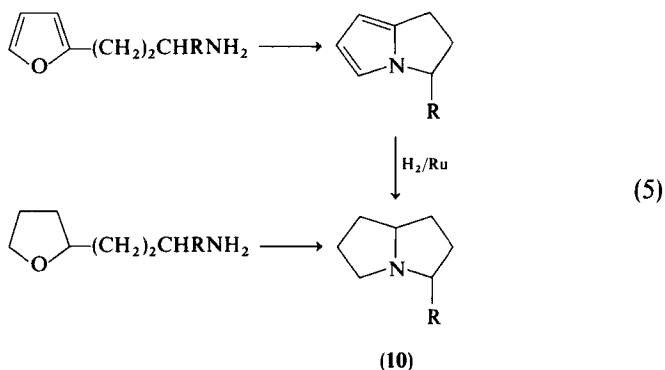
Surzur and Stella have utilized the radical bicyclization of ethylenic *N*-chloroamines to produce pyrrolizidines functionalized at C-2.¹⁴ Reaction of allylamine with 1-bromopent-4-ene, followed by chlorination, gave the *N*-chloroamine (11). Treatment of 11 with aqueous acetic acid and titanium(III)

¹¹ I. M. Skvortsov and I. V. Antipova, *Khim. Geterotsikl. Soedin.*, 329 (1973) [*CA* 78, 159349 (1973)].

¹² I. M. Skvortsov and I. V. Antipova, *Khim. Geterotsikl. Soedin.*, 1060 (1976) [*CA* 85, 192056 (1976)].

¹³ I. M. Skvortsov and I. V. Antipova, *Tr. Molodykh Uch., Saratov Univ., Vyp. Khim.*, 158 (1971) [*CA* 79, 78496 (1973)]; I. M. Skvortsov and V. M. Levin, *Khim. Geterotsikl. Soedin.*, 947 (1973) [*CA* 79, 125702 (1973)]; I. M. Skvortsov, I. V. Antipova, Yu. A. Pentin, T. X. Hoang, and S. V. Vasil'kovskii, *Khim. Geterotsikl. Soedin.*, 1087 (1975) [*CA* 83, 192988 (1975)]; I. M. Skvortsov and S. A. Kolesnikov, *Khim. Geterotsikl. Soedin.*, 484 (1976) [*CA* 85, 62897 (1976)].

¹⁴ J.-M. Surzur and L. Stella, *Tetrahedron Lett.*, 2191 (1974).

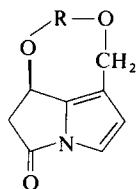


chloride under nitrogen at -10° gave a 60% yield of 2-chloromethylpyrrolizidine (12). The reaction shown in Eq. (6) is thought to occur by initial chlorine abstraction, followed by radical cyclization to form a five-membered ring. This radical (13) undergoes a second sterically favored ring closure to yield 12. This process proceeds more readily than the capture of a chlorine radical to produce a monocyclic system [Eq. (6)]. Approximately equal amounts of exo- and endo-chloromethyl derivatives (12) are formed.

C. INTRAMOLECULAR ACYLATION OF AMINO ACIDS

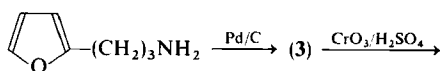
Cyclization of 2-substituted pyrrole or pyrrolidine derivatives with carboxyl functions γ to the nitrogen readily produces oxopyrrolizidine compounds. These cyclic amides can then be reduced to pyrrolizidines by a variety of reagents. This method could now assume greater importance owing to the recent discovery by Bohlmann and co-workers of naturally

occurring lactams of the general structure **14** in the pyrrolizidine series.¹⁵

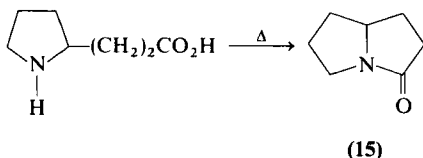


(14)

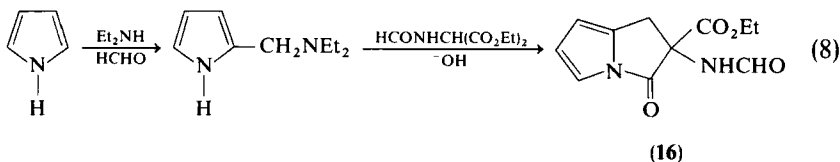
Russian workers have shown that the high pressure hydrogenation of 3-(2'-furyl)-1-propylamine gave moderate yields of the recycled pyrrolidine-propanol (**3**).¹⁶ Cyclization to pyrrolizidine (**1**) was achieved with hydrobromic acid (Section II,B). Alternatively, 3-oxopyrrolizidine (**15**) was formed as outlined in Eq. (7). Further alkyl-substituted compounds of type **15** were also prepared from suitable alkyl-substituted pyrrolidines. Some of these products were sedatives.



(7)



(15)



(16)

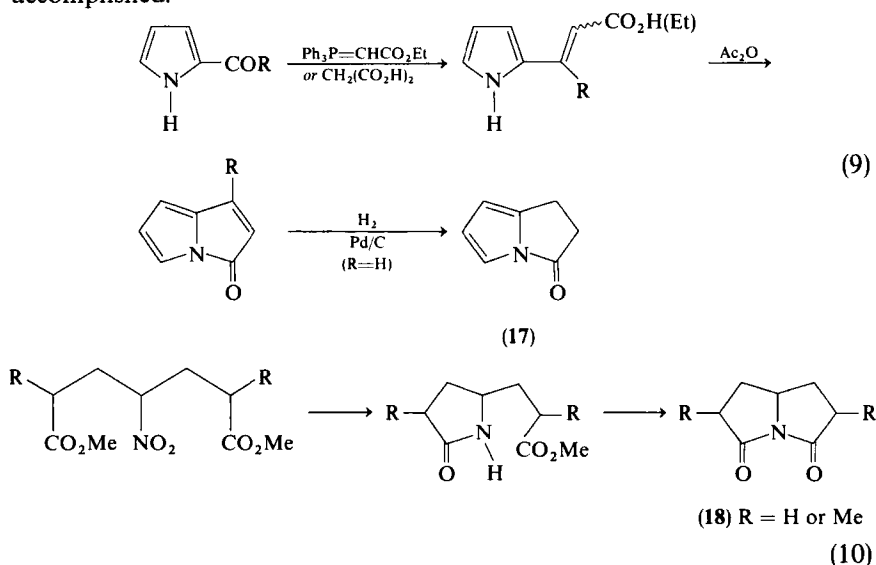
Pyrrole derivatives have been used in two different methods to construct the dihydropyrrolizinone system. Hanck and Kutscher¹⁷ prepared the formamido-substituted compound (**16**) in 70% overall yield from pyrrole [Eq. (8)]. In the second method, Flitsch and Neumann made use of the

¹⁵ F. Bohlmann, C. Zdero, and M. Grenz, *Chem. Ber.* **110**, 474 (1977); F. Bohlmann, K.-H. Knoll, C. Zdero, P. K. Mahanta, M. Grenz, A. Suwita, D. Ehlers, N. L. Van, W.-R. Abraham, and A. A. Natu, *Phytochemistry* **16**, 965 (1977).

¹⁶ A. A. Ponomarev, M. V. Noritsina, and A. P. Kriven'ko, *Khim. Geterotsikl. Soedin.*, 1051 (1970) [*CA* **75**, 48802 (1971)]; M. V. Noritsina, *Issled. Obl. Geterotsikl. Soedin.*, 49 (1971) [*CA* **77**, 139702 (1972)].

¹⁷ A. Hanck and W. Kutscher, *Hoppe-Seyler's Z. Physiol. Chem.* **338**, 272 (1964).

Wittig reaction.¹⁸ The cyclization step [Eq. (9)] proceeded in rather poor yield, but reduction to the 1,2-dihydro compound (17) was readily accomplished.



Hydrogenation of nitropimelates under drastic conditions has been widely used for the construction of simple alkyl-substituted pyrrolizidines.¹ Colonge and Pouchol¹⁹ have developed a milder route to 3,5-dioxopyrrolizidines starting from 4-nitropimelate esters [Eq. (10)]. Raney nickel reduction of the nitroester gave a pyrrolidone that afforded the 3,5-dioxo compound (18) on distillation.

Danishefsky and co-workers have used activated cyclopropanes to promote intramolecular alkylation of an amino function, followed by lactam formation to provide a new entry to the pyrrolizidine ring system.²⁰ This route is outlined in Scheme 1. Cyclopropanation of the phthalimido-olefin (19) was achieved with dimethyldiazomalonate in the presence of copper bronze. Treatment of the cyclopropane derivative (20) with hydrazine released the amine, which gave the lactam ester (21) in quantitative yield. This corresponds to intramolecular homoconjugate addition entirely in the spiro mode.²¹ It seems reasonable that the first step in this process is internal alkylation of the amine by the activated cyclopropane. The alternative

¹⁸ W. Flitsch and U. Neumann, *Chem. Ber.* **104**, 2170 (1971).

¹⁹ J. Colonge and J.-M. Pouchol, *Bull. Soc. Chim. Fr.*, 598 (1962).

²⁰ S. Danishefsky and J. Dynak, *J. Org. Chem.* **39**, 1979 (1974).

²¹ S. Danishefsky, J. Dynak, W. Hatch, and M. Yamamoto, *J. Am. Chem. Soc.* **96**, 1256 (1974).

Cyclopropanation was carried out as before, utilizing the syn-addition of carbenoids to double bonds. Dephthaloylation of the activated cyclopropane (**25**) did not proceed as readily as with **20** → **21**, but was finally achieved using excess hydrazine. Intramolecular opening of **25** then occurred with complete inversion of configuration to give the pyrrolizidine hydrazide (**26**). Deacylation of **26** produced a salt containing a γ -lactone function which was formulated as **27**. The lactam function was regenerated using sodium methoxide, and a final reduction step afforded (\pm)-isoretronecanol (**22**). Analogous treatment of the *Z*-isomer of **24** produced (\pm)-trachelanthamidine (**23**). A similar approach, using activated cyclopropanes, has recently been exploited to provide an entry to the pyrroloindole system,²³ and the mitosanes,²⁴ which are related to the naturally occurring mitomycins.

D. REDUCTIVE CYCLIZATION

Pyrrolizidines are produced by hydrogenation of a surprising variety of precursors. Two illustrative methods have been patented. Pyrrolizidine (**1**) itself was prepared from succinic anhydride in two steps, each giving about 80% yields.²⁵ The spirodilactone (**28**) was obtained by heating succinic anhydride at 250° for 3 hours with strong base [Eq. (11)]. High pressure hydrogenation of this intermediate in the presence of ammonia and a complex catalyst gave pyrrolizidine (**1**). In the second example, the tetramethylpyrrolizidine (**29**) was formed from the dinitrile (**30**) by hydrogenation with Raney nickel catalyst in an oscillating autoclave.²⁶ The mixture of products obtained [Eq. (12)] was not separated, but further reduced over platinum oxide and Raney nickel to give **29**. The yield in each reduction step was about 60%.

Pyrrolizidine was also prepared directly from the previously discussed pyrrolidinepropanol intermediate (**3**) (Section II,B) by treatment with Raney nickel in 49% yield.⁷ This reductive cyclization gave a lower yield of pyrrolizidine than that obtained with indolizidine or quinolizidine under similar conditions.²⁷ It is suggested that this is due to steric effects in the formation of the presumed iminium ion intermediate (**31**), which could not be formed from pyrrolizidine even under forcing conditions (but see Section II,G).

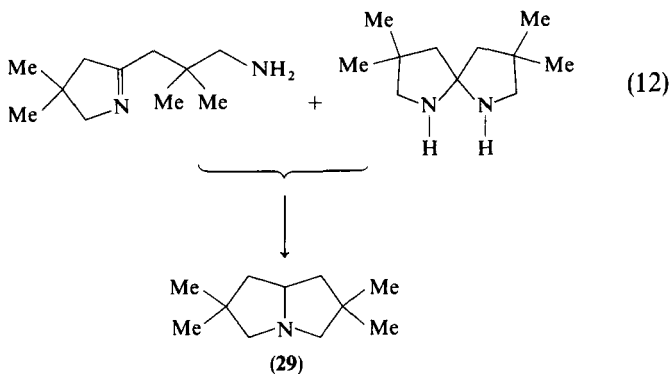
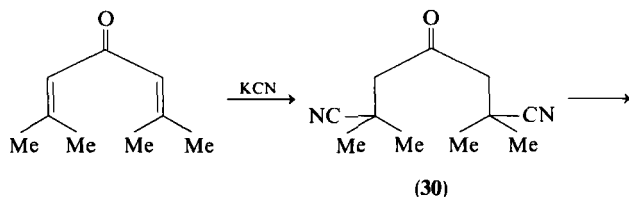
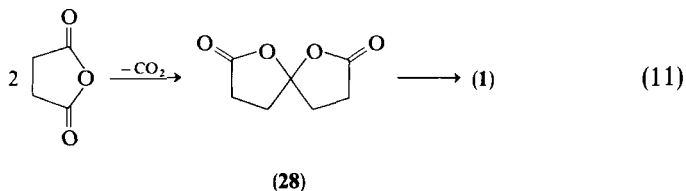
²³ S. Danishefsky and R. Doehner, *Tetrahedron Lett.*, 3029 (1977).

²⁴ S. Danishefsky and R. Doehner, *Tetrahedron Lett.*, 3031 (1977).

²⁵ D. Mesch, D. Voges, and S. Winderl, German Patent 2,136,866 [*CA* **78**, 111114 (1973)].

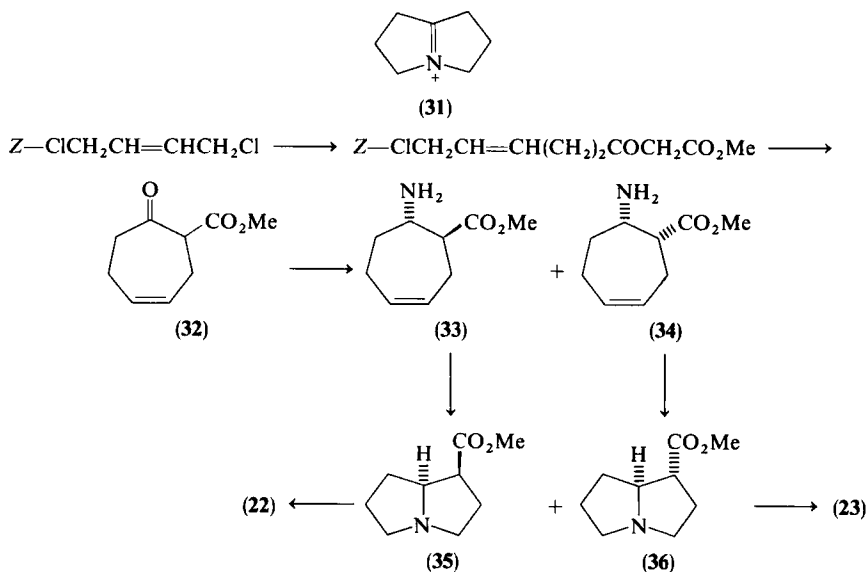
²⁶ A. R. Kittleson, French Patent 1,560,964 [*CA* **72**, 78864 (1970)].

²⁷ M. G. Reinecke and L. R. Kray, *J. Org. Chem.* **29**, 1736 (1964).



Reductive cyclization has been used in a novel, recent synthesis of the alkaloids (\pm)-isoretronecanol (**22**) and (\pm)-trachelanthamidine (**23**) by Borch and Ho.²⁸ Condensation of the dianion derived from methyl acetoacetate with *Z*-1,4-dichlorobut-2-ene, followed by cyclization with sodium methoxide yielded the cycloheptenone ester intermediate (**32**) (Scheme 2). Reductive amination of this ketoester with sodium cyanoborohydride and ammonium nitrate gave a mixture of the diastereoisomeric aminoesters **33** and **34**. Oxidation with osmium tetroxide and periodate, followed by reductive cyclization, again using sodium cyanoborohydride, gave the two pyrrolizidine esters **35** and **36** in a ratio of 1:2 [gas-liquid chromatography (GLC) analysis]. The esters were separated by preparative layer chromatography, and lithium aluminum hydride reduction of the individual esters gave the two pyrrolizidine alkaloids **22** and **23**.

²⁸ R. F. Borch and B. C. Ho, *J. Org. Chem.* **42**, 1225 (1977).



SCHEME 2

E. DIECKMANN CONDENSATION OF PYRROLIDINE DERIVATIVES

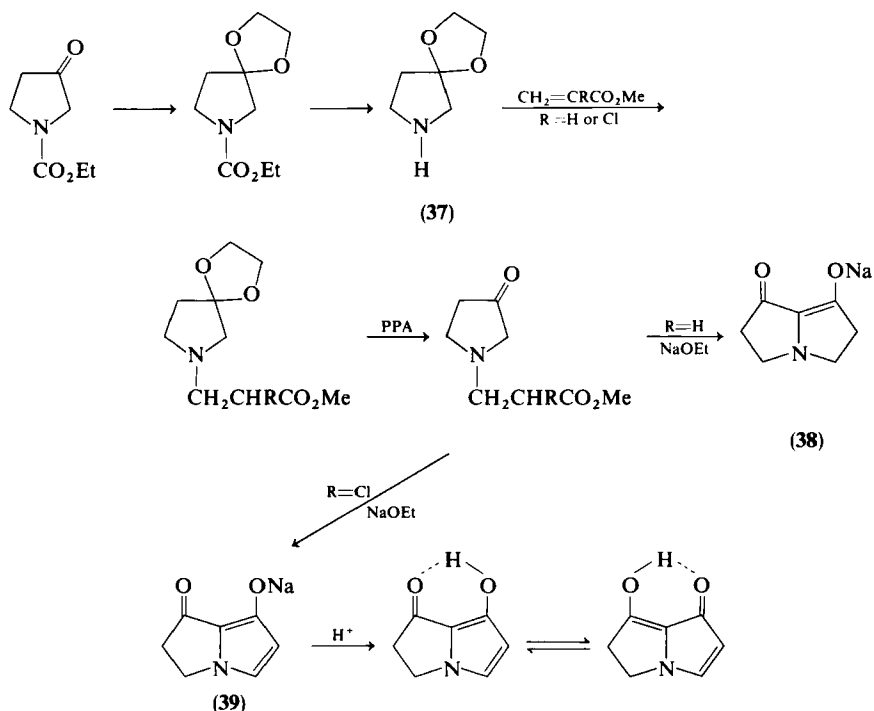
Synthesis of pyrrolizidines by Dieckmann condensation continues to receive wide attention. It is a useful method for producing pyrrolizidines with oxygen substituents and has been exploited in a number of syntheses by Viscontini and co-workers. For their attempted preparation of 1,7-dioxopyrrolizidine, the very unstable 3-oxopyrrolidine was required as an intermediate.²⁹ This compound was stabilized by ketalization (37), and by this means *N*-substituted 3-oxopyrrolidines are readily accessible. The 1,7-dioxopyrrolizidine was synthesized as the sodium enolate (38) as shown in Scheme 3. The dione itself is unstable and could not be isolated. Analogous Michael addition of the pyrrolidine (37) to α -chloroacrylic ester gave the corresponding 5,6-dihydropyrrolizine as the sodium salt (39).³⁰ Treatment of this salt with acid produced a very stable H-bonded aromatic species.

Viscontini and Gillhof-Schaufelberger extended their interest in dihydropyrrolizines by synthesizing (\pm)-dehydroheliotridine (40).³¹ The toxicity of some pyrrolizidine alkaloids is believed to be due to the formation of com-

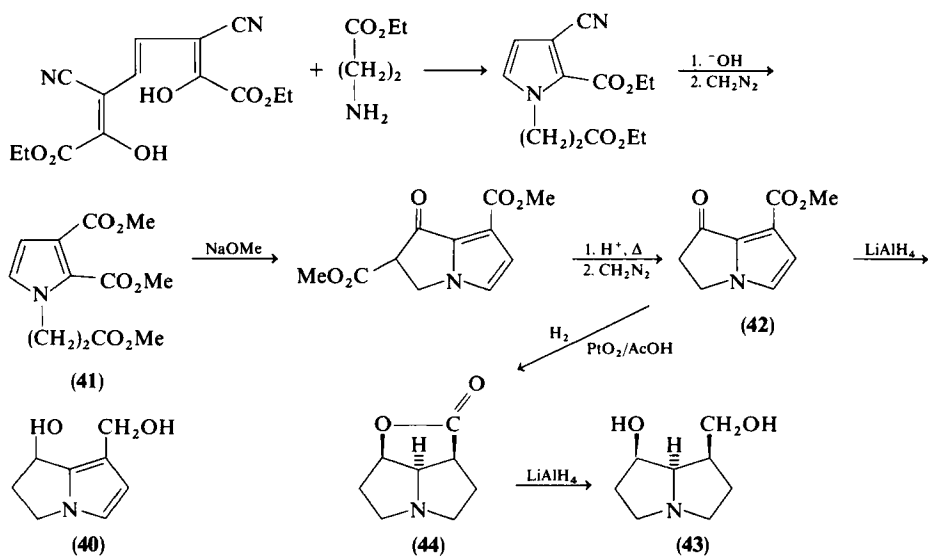
²⁹ M. Viscontini and H. Buehler, *Helv. Chim. Acta* **50**, 1289 (1967).

³⁰ M. Viscontini and H. Buehler, *Helv. Chim. Acta* **53**, 351 (1970).

³¹ M. Viscontini and H. Gillhof-Schaufelberger, *Helv. Chim. Acta* **54**, 449 (1971).



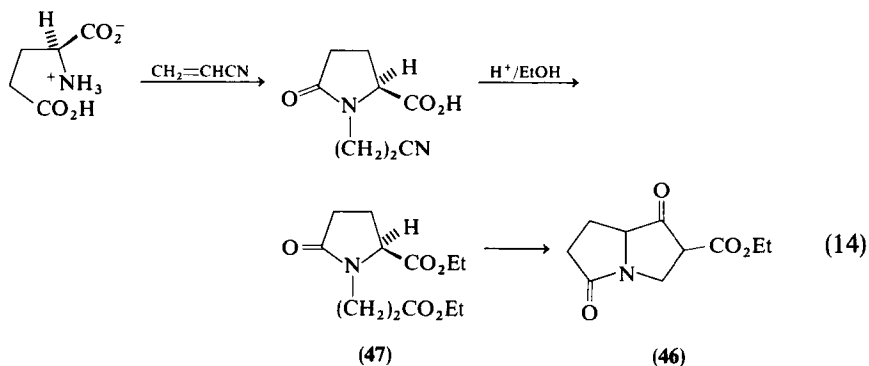
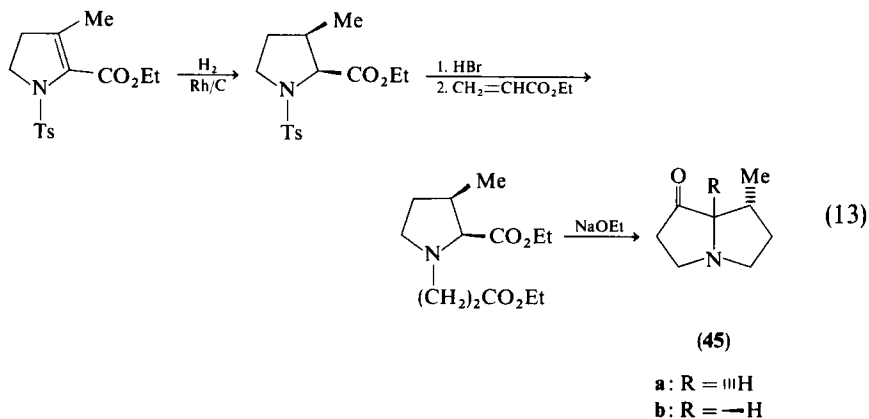
SCHEME 3



SCHEME 4

pounds of type **40** in the liver. The pyrrole triester (**41**) was prepared as outlined in Scheme 4. Dieckmann cyclization of the triester, followed by hydrolysis, decarboxylation, and methylation, gave the dihydropyrrolizine (**42**). Reduction of this ketoester gave (\pm)-dehydroheliotridine (**40**). The useful dihydropyrrolizine intermediate (**42**) was also used for the synthesis of the alkaloid (\pm)-platynecine (**43**) by Viscontini and Buzek³² (Scheme 4). The (\pm)-lactone (**44**) was obtained as the major product (40%) on catalytic hydrogenation of **42**. Further reduction gave (\pm)-platynecine (**43**) (60%).

Meinwald and Ottenheim required 1-methyl-7-oxopyrrolizidine (**45**) in connection with their studies on structural analogs of the male butterfly pheromone 1-methyl-7-oxo-5,6-dihydropyrrolizine.³³ The analog was synthesized by a shorter route than that previously described.³⁴ From the intramolecular cyclization process shown in Eq. (13), a 19:1 mixture of



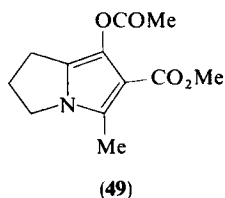
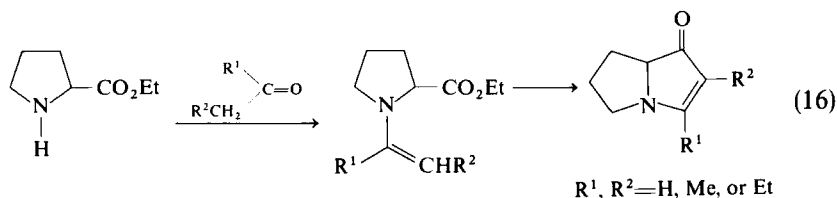
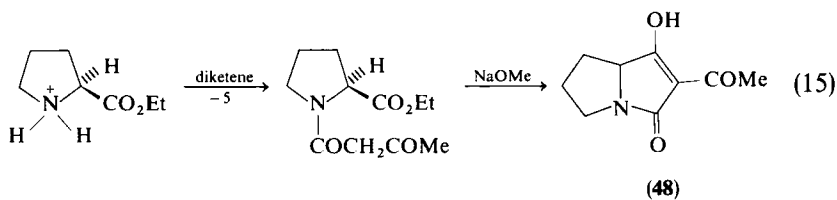
³² M. Viscontini and H. Buzek, *Helv. Chim. Acta* **55**, 670 (1972).

³³ J. Meinwald and H. C. J. Ottenheim, *Tetrahedron* **27**, 3307 (1971).

³⁴ R. Adams and N. J. Leonard, *J. Am. Chem. Soc.* **66**, 257 (1944).

diastereoisomers (**45**) was obtained, which was separated by preparative GLC. It was suggested that the major component is **45a**, because the methyl substituent is then in the more stable *exo*-position.

Pyrrolizidines compounds have been produced in connection with syntheses of other types of natural products. For example, Gensler and Hu³⁵ prepared the dioxopyrrolizidine ester (**46**) as an intermediate in the synthesis of (\pm)-slaframine, an indolizidine alkaloid obtained from cultures of *Rhizoctonia leguminicola*. The pyrrolidone ester (**47**), prepared from L-glutamic acid [Eq. (14)], was optically active, but the cyclized product, formed in quantitative yield from **47**, was completely racemized. The synthesis of 2-acetyl-1,3-dioxopyrrolizidine (**48**) was carried out by Kruger and Arndt to assist with their investigations on model compounds aimed toward the total synthesis of α -cyclopiazonic acid, the main toxic principle of *Penicillium cyclopium*.³⁶ The spectra of the product (**48**) obtained in 30% overall yield was typical of an intramolecularly H-bonded enolized β -



diketone [Eq. (15)]. A related method, involving intramolecular cyclization of an enamine with an ester was utilized by Hickmott and Woodward to

³⁵ W. J. Gensler and M. W. Hu, *J. Org. Chem.* **38**, 3848 (1973).

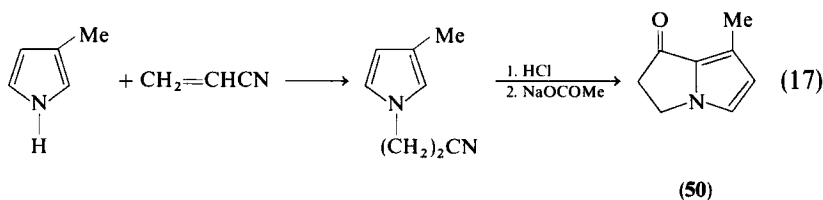
³⁶ P. E. Kruger and R. R. Arndt, *J. S. Afr. Chem. Inst.* **26**, 132 (1973).

prepare dihydropyrrolizine derivatives³⁷ [Eq. (16)]. In a similar fashion, use of methyl acetoacetate in place of the simple acyclic ketones gave the dihydropyrrolizine (49).

In a recent series of papers, Schnekenburger and co-workers have repeated several existing methods for the construction of 1- and 2-hydroxypyrrolizidines and 1- and 2-hydroxymethylpyrrolizidines, using mainly the Dieckmann cyclization of pyrrole or pyrrolidine diesters.³⁸ The diastereoisomers produced were separated by distillation or chromatography, and the racemates were resolved by standard techniques.

F. HOUBEN-HOESCH-TYPE CYCLIZATIONS

Intramolecular electrophilic substitution of a pyrrole by a nitrile under acidic conditions generates a dihydropyrrolizine after hydrolysis of the iminium ion intermediate. This type of cyclization has received considerable attention.¹ Brauholtz *et al.* demonstrated that improved yields (70%) in the cyclization step were effected with a melt of the chlorides of aluminum, potassium, and sodium, but the conditions were extremely critical.³⁹ Meinwald and Meinwald used this method for their preparation of the dihydropyrrolizone (50).⁴⁰ This confirmed the structure of the major component of the hairpencil secretion of the male tropical butterfly *Lycorea ceres ceres*. None of the isomeric 2-methyl compound was formed during this synthesis [Eq. (17)]. It is suggested that the 3-methyl group of pyrrole activates the adjacent 2-position sufficiently to promote regiospecific intramolecular electrophilic substitution.



³⁷ P. W. Hickmott and K. N. Woodward, *J.C.S. Perkin I*, 904 (1976).

³⁸ J. Schnekenburger and E. Breit, *Arch. Pharm. (Weinheim)* **310**, 152 (1977); J. Schnekenburger and E. Breit, *Arch. Pharm. (Weinheim)* **310**, 161 (1977); J. Schnekenburger and H. Vollhardt, *Arch. Pharm. (Weinheim)* **310**, 177 (1977); J. Schnekenburger and H. Vollhardt, *Arch. Pharm. (Weinheim)* **310**, 186 (1977).

³⁹ J. T. Brauholtz, K. B. Mallion, and F. G. Mann, *J. Chem. Soc.*, 4346 (1962).

⁴⁰ J. Meinwald and Y. C. Meinwald, *J. Am. Chem. Soc.* **88**, 1305 (1966).

G. TRANSANNULAR REACTIONS

This route to pyrrolizidines depends largely on the availability of 1-azacyclooctane derivatives with oxygen functions at the 5-position. Such compounds readily undergo transannular reactions to give pyrrolizidines. The development of transannular reactions, together with the use of microbiological systems to introduce oxygen functions at unactivated sites, has been one of the most promising areas of progress since the last review was written. Much of the early work on transannular reactions was carried out by Leonard.⁴¹ Salts of 1-alkyl-1-azacyclooctan-5-ones (**51**) generally exist in the transannular form (**52**).⁴² These salts do not show infrared (IR) absorption in the region $1620\text{--}1800\text{ cm}^{-1}$, but hydroxyl absorption is present at 3290 cm^{-1} . Furthermore, the nuclear magnetic resonance (NMR) spectra show that a singlet is obtained for the benzyl protons of **52**. Splitting would be expected if the nitrogen were protonated. The hydroxyl proton is also observable in the NMR spectra.

Pyrrolizidines are also generated from the corresponding azacyclooctanol (**53**). For example, as part of the investigation of the possible transannular cyclization of olefinic cyclic amines, Sisti and Lohner⁴³ found that **53** did not undergo dehydration as they expected, but on heating in hydriodic acid formed the pyrrolizidine salt (**54**) in high yield (82%). The driving force for these acid-catalyzed transannular reactions is apparently the close steric proximity of the nitrogen and the oxygen-bearing carbon, which is readily demonstrated by models.

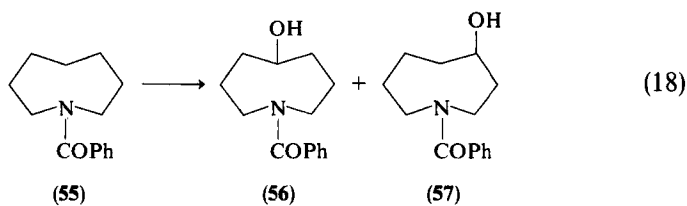
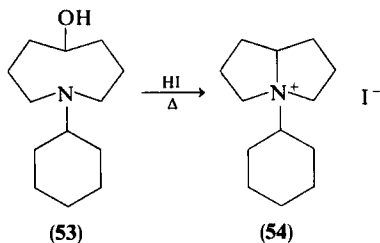
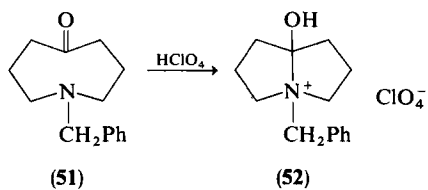
A particularly interesting development in this area has been the introduction of oxygen functions by microbiological oxygenation of the macrocyclic amine precursors. This has been investigated by Johnson *et al.* using *Sporotrichum sulfurescens*.⁴⁴ The benzoylated amine (**55**), requires an optimum spacing of 5.5 \AA between the electron-rich center of the substrate (the carbonyl oxygen) and the point of enzymic oxygenation. The major product (**56**) from the microbial oxidation was obtained in 40–50% yield, together with about 15% of the isomeric compound (**57**), with oxygen at the adjacent carbon atom [Eq. (18)]. The hydroxylated mixture was further oxidized chemically to the corresponding ketones for ease of work-up and separation. This method permits the insertion of an oxygen function at a position that is extremely difficult to functionalize chemically. The major

⁴¹ N. J. Leonard, *Rev. Chem. Prog.* **17**, 243 (1956).

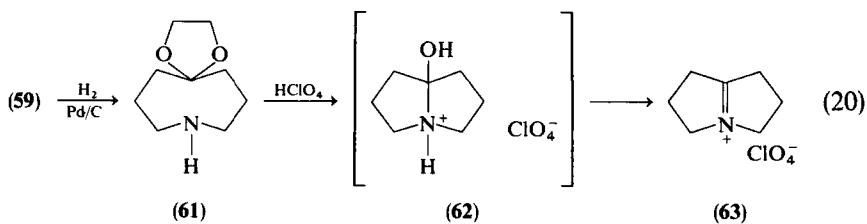
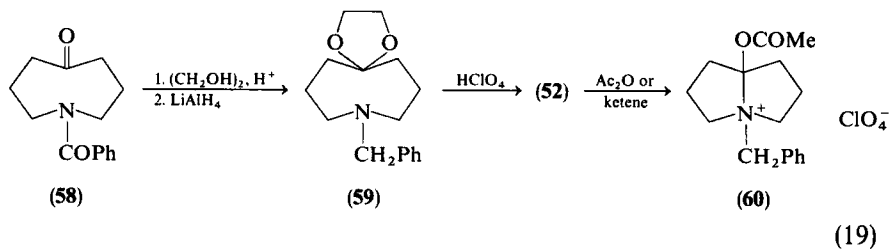
⁴² N. J. Leonard and J. A. Klainer, *J. Org. Chem.* **33**, 4269 (1968).

⁴³ A. J. Sisti and D. L. Lohner, *J. Org. Chem.* **32**, 2026 (1967).

⁴⁴ R. A. Johnson, M. E. Herr, H. C. Murray, and G. S. Fonken, *J. Org. Chem.* **33**, 3187 (1968).



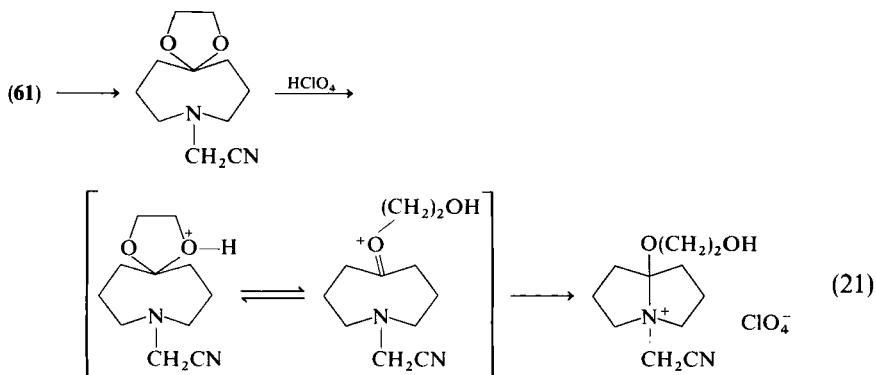
ketonic product (58) possesses the necessary features to undergo a transannular reaction, once the nitrogen function is altered to become nucleophilic in character. Ketalization (90%), followed by reduction (87%), generated a potential aminoketone (59) of the type studied earlier by Leonard *et al.* in



their work on transannular interactions in eight-membered ring systems.⁴⁵ Johnson *et al.*⁴⁴ showed that treatment of the protected intermediate (59) or the free ketone (51) with perchloric acid yielded a perchlorate salt (52) that was isolable. The hydroxyl group generated was acetylated using either acetic anhydride⁴⁴ or ketene⁴² [Eq. (19)]. The salt (60) is a powerful acetylating reagent.

Most transannular compounds are derived from tertiary amines. Johnson *et al.*⁴⁴ debenzylated their protected intermediate (59) to produce a secondary amine (61), which formed a salt with aqueous perchloric acid [Eq. (20)]. The IR spectrum of this product showed absorption at 1690 cm^{-1} , but not in the hydroxyl region, indicating that the presumed transannular salt (62) has been dehydrated to an iminium salt (63).

In further work, Johnson investigated the interception of ketal hydrolysis by a transannular amine reaction.⁴⁶ The debenzylated protected intermediate (61) was cyanomethylated in 85% yield [Eq. (21)]. Because of the reduced



basicity of the tertiary amine, treatment with acid allowed protonation of the ketal oxygen to compete with protonation of the nitrogen. Then the proximity of the nitrogen to the potential carbonium ion permitted the nitrogen to intercept the hydrolysis, either by attack on the carbonium ion or via a concerted process [Eq. (21)]. Johnson⁴⁶ also prepared a transannular enamine from the useful intermediate (58). Witting reaction of 58 gave an amide (41%) which produced the desired enamine (64) on reduction (78%). It was shown that this could react either as a transannular enamine or as a typical amine [Eq. (22)].

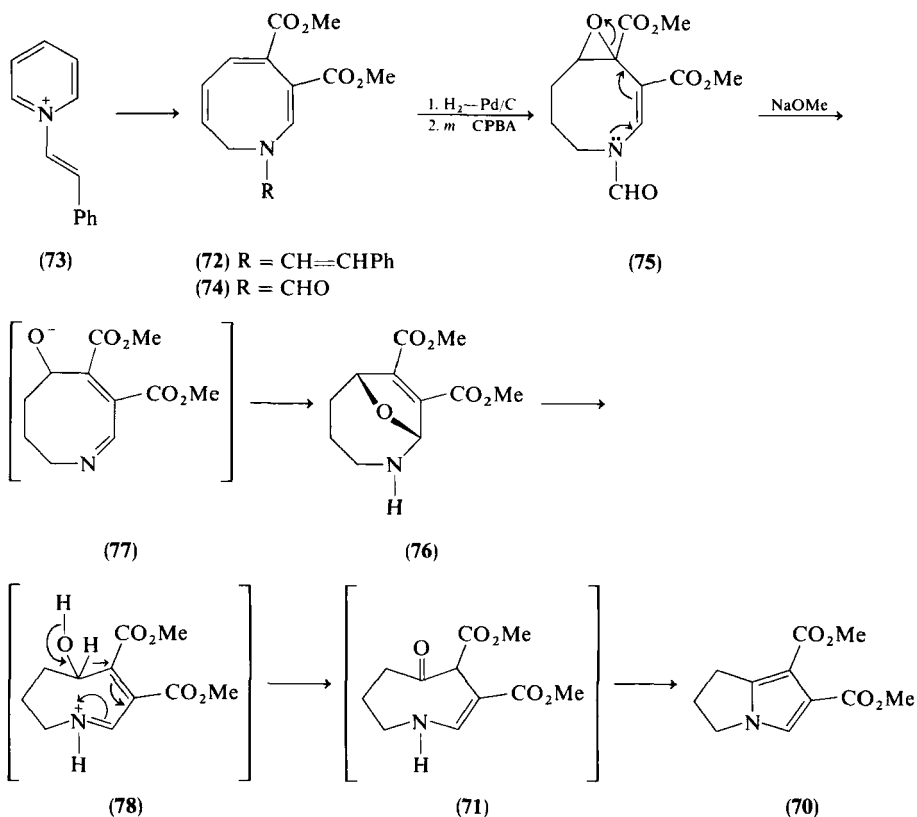
A transannular reaction has been successfully applied to the stereo-specific synthesis of (\pm)-isoretronecanol (22) by Leonard and Sato.⁴⁷ The

⁴⁵ N. J. Leonard, M. Oki, and S. Chiaverelli, *J. Am. Chem. Soc.* **77**, 6234 (1955).

⁴⁶ R. A. Johnson, *J. Org. Chem.* **37**, 312 (1972).

⁴⁷ N. J. Leonard and T. Sato, *J. Org. Chem.* **34**, 1066 (1969).

dimethyl acetylenedicarboxylate to a 1,2-dihydropyridine, obtained by borohydride reduction of the corresponding pyridinium salt (**73**). Selective ozonolysis of the exocyclic double bond of **72** and reductive work-up gave the formamide derivative (**74**). Further selectivity was achieved in reducing one double bond, and epoxidizing another to yield the epoxyazocine (**75**). Deformylation of **75** produced a bicyclic aminoether (**76**) by transannular

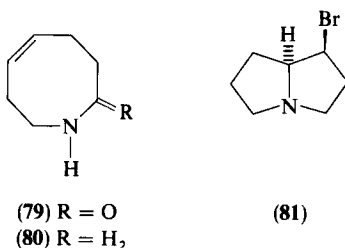


SCHEME 5

addition of the presumed alkoxyanion intermediate (**77**). Finally, acid-catalyzed opening of **76** with pyridinium chloride generated the diester (**70**), possibly by a mechanism involving a hydride shift within the iminium ion (**78**), followed by cyclodehydration of the azacyclooctanone (**71**). An overall yield of <20% from **73** (or <3% from styrene), was obtained for the only pyrrolizidine synthesized by this somewhat lengthy route. The use of this route to produce a range of highly functionalized pyrrolizidines, as envisaged by the authors, appears therefore to have limited potential. Furthermore,

it should be noted that crystalline **70** has been prepared in a one-step process in 90% yield by 1,3-dipolar addition of dimethyl acetylenedicarboxylate to *N*-formylproline⁴⁹ (see Section II.I).

A transannular route to 1-substituted pyrrolizidines has recently been reported by Wilson and Sawicki.⁵⁰ The lactam (**79**) was prepared by Beckmann rearrangement of the oxime *p*-toluenesulfonate of cyclohept-4-enone. Reduction with lithium aluminum hydride gave the amine (**80**), which on treatment with bromine yielded the 1-bromopyrrolizidine (**81**) in one stereospecific step (95%). The stereochemistry of the product corresponds to a disfavored *exo*-mode of cyclization⁵¹ by attack of the nitrogen on the bromonium ion. Further modification of this route to produce naturally occurring alkaloids would appear feasible, but has not yet been reported.



A final example of the production of pyrrolizidines by transannular reaction is due to Edwards *et al.*⁵² Reactions of *N*-chloroazacyclooctane with various silver species were shown to give pyrrolizidine (**1**) in yields in excess of 70%. The mechanisms of these reactions are in some doubt. Best yields were obtained with silver oxide under nitrogen, and the transannular reaction with Ag(I) species is probably a heterolytic process involving added base. However, the reaction was readily stopped by the radical scavenger oxygen. This suggests that a homolytic chain reaction process is operative, initiated by traces of silver.

H. WITTIG REACTIONS

Reaction of vinyl Wittig reagents with carbonyl-substituted pyrroles has been used to generate the pyrrolizine ring system, from which pyrrolizidines are available by reduction. In this way, Schweizer and Light⁵³ prepared

⁴⁹ D. J. Robins and S. Sakdarat, unpublished work (1977).

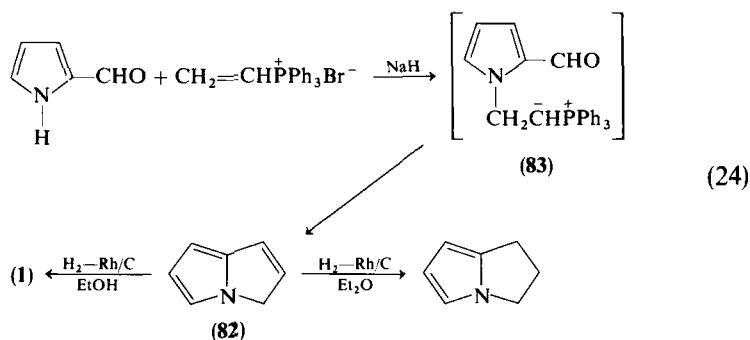
⁵⁰ S. R. Wilson and R. A. Sawicki, *J. Chem. Soc., Chem. Commun.*, 431 (1977).

⁵¹ J. E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 734 (1976).

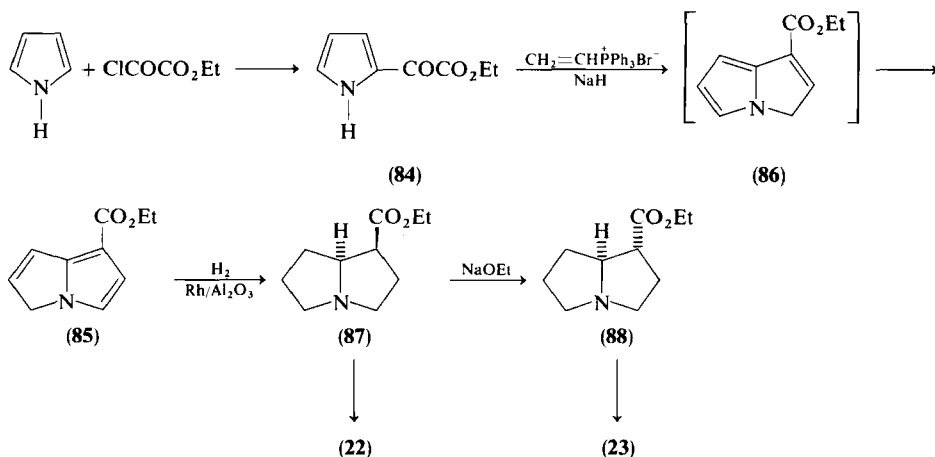
⁵² O. E. Edwards, D. Vocelle, and J. W. ApSimon, *Can. J. Chem.* **50**, 1167 (1972).

⁵³ E. E. Schweizer and K. K. Light, *J. Am. Chem. Soc.* **86**, 2963 (1964); E. E. Schweizer and K. K. Light, *J. Org. Chem.* **31**, 870 (1966).

3*H*-pyrrolizine (**82**) in 87% yield. Formation of an ylid (**83**) by Michael addition probably precedes the intramolecular Wittig reaction [Eq. (24)]. For the catalytic reduction, rhodium on charcoal was used, and the choice of solvent was critical. With ether, partial hydrogenation was accomplished, and full reduction took place when ethanol was present [Eq. (24)]. An analogous reaction with the same vinyl salt and 2-acetylpyrrole led to (\pm)-1-methylpyrrolizidine on complete reduction.



A similar approach was utilized by Brandange and Lundin in their synthesis of the endo- and exo-isomers of 1-substituted pyrrolizidines.⁵⁴ The glyoxylate ester (**84**) was prepared at low temperature in an improved yield of 64% (Scheme 6). Wittig reaction of this ester with the allyl salt used by Schweizer and Light,⁵³ gave mainly the pyrrolizine ester (**85**), possibly



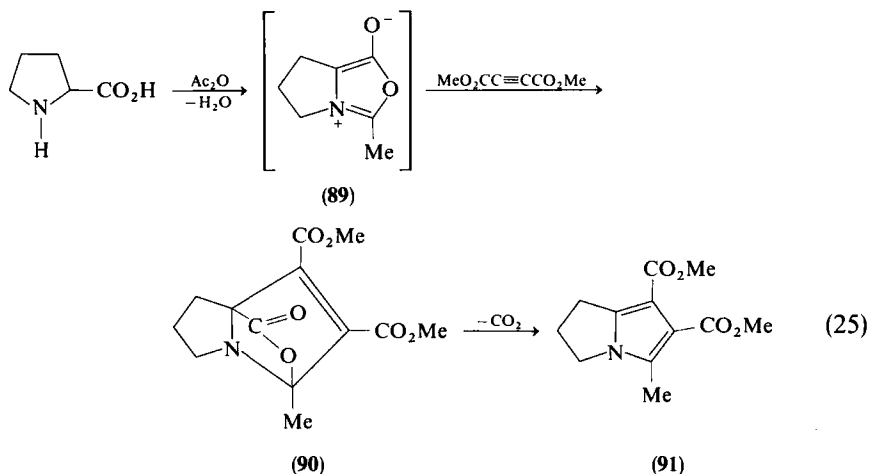
SCHEME 6

⁵⁴ S. Brandange and C. Lundin, *Acta Chem. Scand.* **25**, 2447 (1971).

via the intermediate **86**. The ester mixture was hydrogenated completely over a rhodium on alumina catalyst to yield a mixture of pyrrolizidine esters (**87**) and (**88**), in which the thermodynamically less stable endo-isomer (**87**) predominated. Complete epimerization at C-1 of **87** to the more stable racemate (**88**) is known to proceed in high yield.⁵⁵ Reduction of the separated esters gave the alkaloids (\pm)-isoretronecanol (**22**) and (\pm)-trachelanthamidine (**23**).

I. 1,3-DIPOLAR ADDITION REACTIONS

The high-yielding 1,3-dipolar addition to suitable proline derivatives has been exploited by several groups of workers to produce pyrrolizidines substituted in only one ring. This is one of the shortest and most efficient routes to pyrrolizidines. Huisgen and co-workers began research in this area by studying the 1,3-dipolar addition of alkynes to mesoionic oxazolones to generate *N*-substituted pyrroles.⁵⁶ When L-proline is used as starting material, dihydropyrrolizidines are produced⁵⁷ [Eq. (25)]. The oxazolium oxide (**89**), formed by dehydration of *N*-acetylproline, is not isolable, but is trapped by 1,3-dipolar addition with dimethyl acetylenedicarboxylate to give the tricyclic lactone (**90**). Loss of carbon dioxide from this molecule



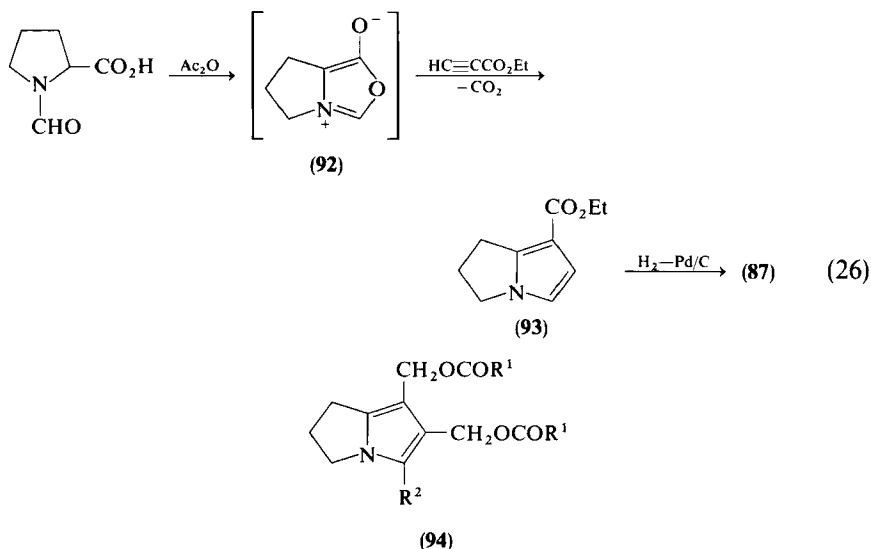
⁵⁵ A. M. Likhoshesterov, V. N. Kulakov, and N. K. Kochetkov, *Zh. Obshch. Khim.* **34**, 2798 (1964) [*CA* **61**, 14734 (1964)].

⁵⁶ R. Knorr and R. Huisgen, *Chem. Ber.* **103**, 2598 (1970).

⁵⁷ R. Huisgen, H. Gotthardt, H. O. Bayer, and F. C. Schaefer, *Chem. Ber.* **103**, 2611 (1970); F. M. Hershenson, *J. Org. Chem.* **40**, 1260 (1975).

produces the pyrrolizine (**91**). This is a facile one-pot reaction—the two reagents are simply heated in acetic anhydride for 1 hour at 130°. It is surprising that this sequence of events takes place without any appreciable side reactions occurring, and gives a high overall yield of 76%. An analogous reaction with dimethyl fumarate produced a mixture of dehydropyrrolizidines.⁵⁸

Based on this strategy, an efficient two-step stereospecific route to 1-substituted pyrrolizidines has been achieved by Pizzornico and Albonico.⁵⁹ An oxazolium oxide (**92**) was generated by dehydration of *N*-formyl-L-proline [Eq. (26)]. This underwent regiospecific 1,3-dipolar addition with ethyl propiolate to give the dihydropyrrolizine ester (**93**) in 90% yield after loss of carbon dioxide. Stereospecific hydrogenation of this ester gave pure racemic ester (**87**) in 93% yield. This ester is the same as that obtained by Brandange and Lundin⁵⁴ and can be transformed into the diastereoisomeric 1-hydroxymethylpyrrolizidines as outlined above (Section II,H).



Several applications of this new approach have recently been reported. A series of pyrrolizidine diesters (**94**) have been synthesized by Anderson and Corey using a range of *N*-acylproline derivatives.⁶⁰ The diesters corresponding to **91** were reduced with lithium aluminum hydride, and the diols were esterified to give **94**. Some of these diesters had antileukemic activity.

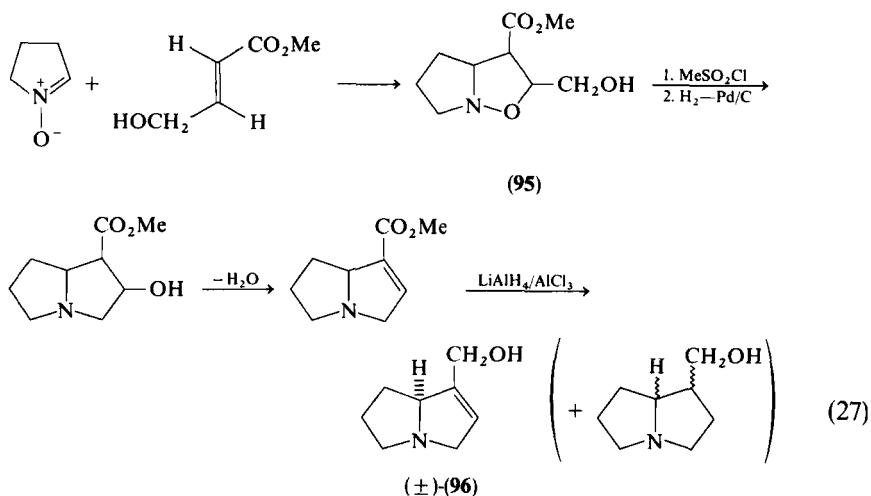
⁵⁸ H. Gotthardt and R. Huisgen, *Chem. Ber.* **103**, 2625 (1970).

⁵⁹ M. T. Pizzornico and S. M. Albonico, *J. Org. Chem.* **39**, 731 (1974).

⁶⁰ W. K. Anderson and P. F. Corey, *J. Med. Chem.* **20**, 812 (1977).

A synthetic approach to mitosenes has been developed by Rebek and Gehret⁶¹ using suitable *N*-acylproline derivatives in the same procedure as outlined in Eq. (25).

The final example in this section is classed as a 1,3-dipolar addition, as this is the key step in the reaction, although actual formation of the pyrrolizidine ring is by an intramolecular alkylation process. Tufariello and Tette⁶² showed that Δ^1 -pyrroline-*N*-oxide added regioselectively in a 1,3-dipolar fashion to the dipolarophile to give an isoxazolidine (**95**) in 80% yield [Eq. (27)]. The pyrrolizidine ring was then formed by hydrogenolysis of the methanesulfonate derivative of **95** in 95% yield. The dehydration and reduction steps were not so efficient, and a mixture of reduction products was obtained. Half of this mixture was (\pm)-supinidine (**96**) and the remainder consisted of fully reduced isomeric 1-hydroxymethylpyrrolizidines.



J. MISCELLANEOUS METHODS

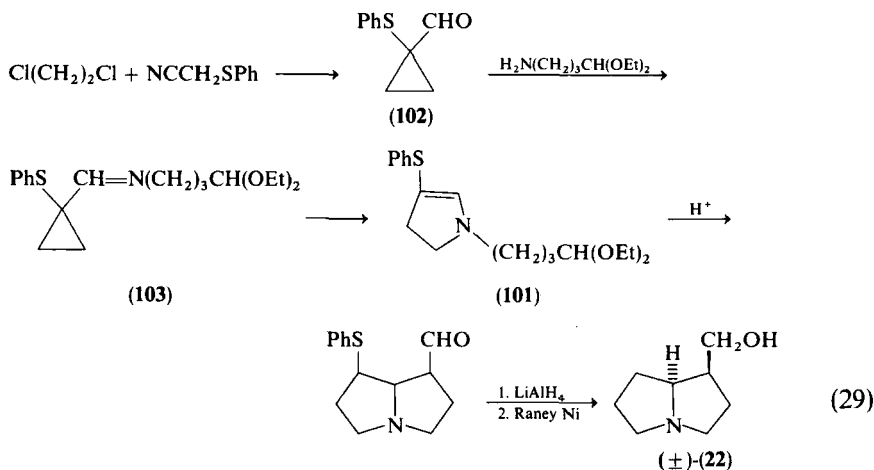
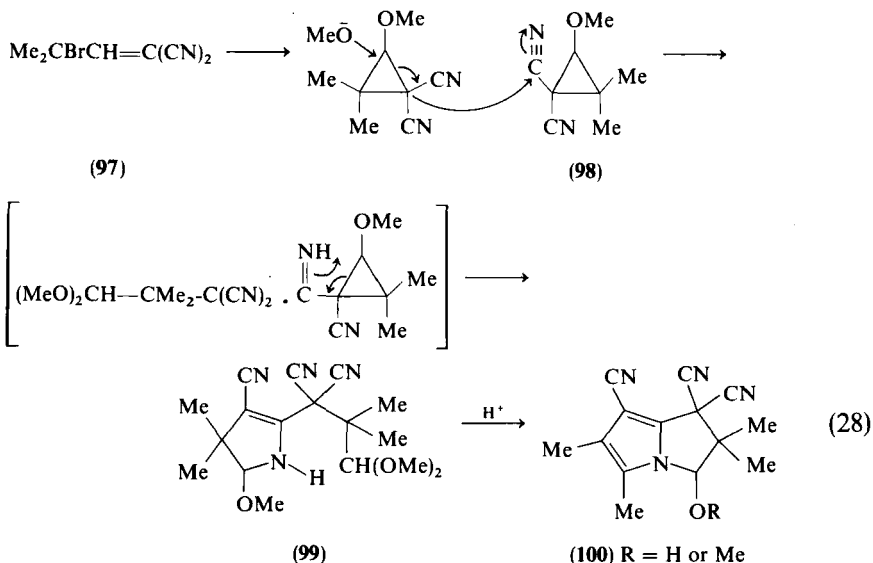
Two entirely different methods utilizing Δ^2 -pyrrolines as intermediates have been published. Storesund and Kolsaker prepared heavily substituted pyrrolizidines by base-catalyzed dimerization of nitriles.⁶³ Initial reaction of the dinitrile starting material (**97**) is presumed to generate a cyclopropane

⁶¹ J. Rebek and J.-C. E. Gehret, *Tetrahedron Lett.*, 3027 (1977).

⁶² J. F. Tufariello and J. P. Tette, *J. Chem. Soc. D*, 469 (1971); J. F. Tufariello and J. P. Tette, *J. Org. Chem.* **40**, 3866 (1975).

⁶³ H. J. Storesund and P. Kolsaker, *Tetrahedron* **30**, 3153 (1974).

(98). Nucleophilic attack at the methoxyl carbon of this compound liberated an open-chain acetal anion, which acted as a powerful nucleophile and attacked a further cyclopropane molecule in a Thorpe reaction [Eq. (28)]. Rearrangement then produced a Δ^2 -pyrroline (99) in an overall yield of 60%. On addition of acid, this Δ^2 -pyrroline aromatized with a simultaneous 1,2-methyl shift and formed the dihydropyrrolizines (100). A mixture of products is obtained because hydrolysis of the acetal function competes with the final ring closure reaction.

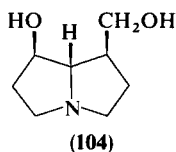
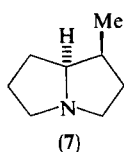
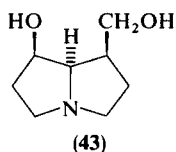


Stevens and co-workers have used the acid-catalyzed rearrangements of cyclopropylimines to give stabilized endocyclic enamine systems.⁶⁴ These can be transformed into bicyclic pyrrolizidine⁶⁵ or indolizidine^{65,66} alkaloids. A stereoselective route to (\pm)-isoretronecanol (**22**) was developed via the key intermediate (**101**). Cyclopropanation of phenylthioacetone nitrile with 1,2-dichloroethane was achieved with lithium diisopropylamide and hexamethylphosphoramide. Selective reduction of the nitrile group was carried out with diisobutyl aluminum hydride to give the aldehyde (**102**) [Eq. (27)]. Schiff base formation and rearrangement of the imine (**103**) by refluxing in xylene containing suspended ammonium chloride gave the pyrroline (**101**). Cyclization with acid, followed by reduction and desulfurization steps yielded (\pm)-isoretronecanol (**22**) of high stereochemical purity (>96% as judged by GLC analysis).

III. Stereochemistry of Pyrrolizidine Bases

A. PYRROLIZIDINE DIOLS

There are four known, naturally occurring fully saturated pyrrolizidine diols. The relative stereochemistry of platynecine (**43**) is known from chemical interconversions of the bases, and the absolute configuration was defined by degradation of heliotridane (**7**) to *S*-(+)-3-methylheptane.⁶⁷



Further work on the stereochemistry of the saturated diols has been carried out by Culvenor and co-workers. The absolute configuration of hastanecine (**104**) was determined by chemical correlation with a diol of known stereochemistry.⁶⁸ The alkaloid lasiocarpine (**105**) yielded 7-angelylheliotridine (**106**) on periodate oxidation. Hydrogenation of this unsaturated ester gave the 1 β -hydroxymethyl isomer (**107**), since it afforded dihydroxyheliotridane (**108**) on hydrolysis (Scheme 7). The absolute con-

⁶⁴ R. V. Stevens, *Acc. Chem. Res.* **10**, 193 (1977).

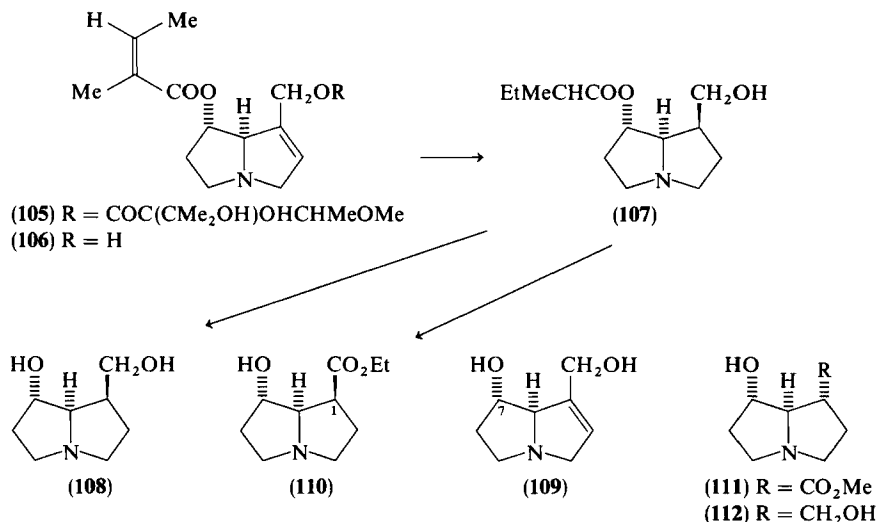
⁶⁵ R. V. Stevens, Y. Luh, and J.-T. Sheu, *Tetrahedron Lett.*, 3799 (1976).

⁶⁶ R. V. Stevens and Y. Luh, *Tetrahedron Lett.*, 979 (1977).

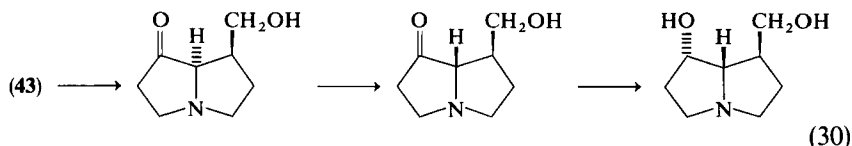
⁶⁷ F. L. Warren and M. E. Von Klemperer, *J. Chem. Soc.*, 4574 (1958).

⁶⁸ A. J. Aasen, C. C. J. Culvenor, and L. W. Smith, *J. Org. Chem.* **34**, 4137 (1969).

figuration of **108** is known⁶⁹; it is a degradation product of heliotridine (**109**). Furthermore, Jones oxidation of **107**, followed by esterification, gave an ester (**110**), which was epimerized at C-1 and transesterified when heated with sodium methoxide to give the thermodynamically more stable isomer (**111**). Lithium aluminum hydride reduction of **111** afforded the diol **112**, which proved to be the enantiomer of hastanecine (**104**).



SCHEME 7

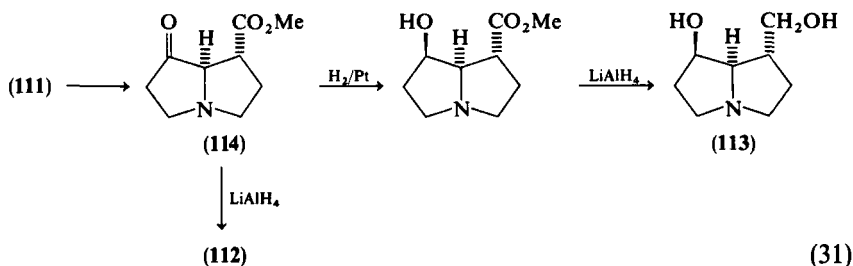


The amino alcohol obtained by hydrolysis of the alkaloid retusine has been shown to be identical with turneforcidine (**113**), even though different specific rotations were originally reported for each compound.⁶⁸ Turneforcidine must have the relative stereochemistry shown in **113**, because it is a different compound from hastanecine (**104**), platynecine (**43**), and dihydroxyheliotridane (**108**). The absolute configuration of **113** was indicated by preparation of the enantiomer of turneforcidine from platynecine (**43**) as outlined in Eq. (30). Proof of the absolute configuration of **113** was obtained by Aasen and Culvenor⁷⁰ by their preparation of turneforcidine from an

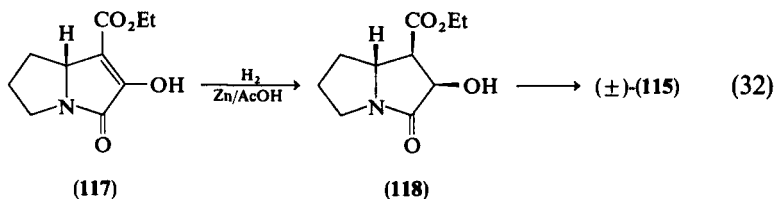
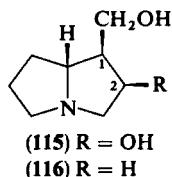
⁶⁹ R. Adams and B. L. Van Duuren, *J. Am. Chem. Soc.* **76**, 6379 (1954).

⁷⁰ A. J. Aasen and C. C. J. Culvenor, *Aust. J. Chem.* **22**, 2657 (1969).

intermediate used in the synthesis of the (+)-enantiomer of hastanecine (**112**). Jones oxidation of **111**, followed by stepwise reduction gave a compound that was identical with turnefordine [Eq. (31)]. Complete reduction of the ketoester (**114**) gave the (+)-enantiomer of hastanecine (**112**).



Macronecine (**115**) was previously shown to have the 1β -hydroxymethyl and 8β -hydrogen substituents by Danilova and Utkin in their degradation of macronecine to laburnine (**116**).⁷¹ The position of the second hydroxy function at C-2 was indicated by NMR data, and the coupling constants were in best agreement with a 2β -hydroxy group.⁷² The synthesis of macronecine (**115**) by Aasen and Culvenor confirmed its structure and relative configuration.⁷² The pyrrolizidine ester (**117**), synthesized earlier by Adams *et al.*⁷³ was catalytically reduced to give a major product (**118**), formed by addition of the hydrogen atoms from the less sterically hindered face. A further reduction step [Eq. (32)] gave a saturated racemate which was resolved via



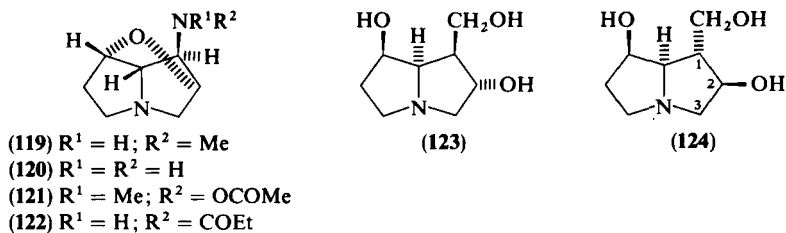
⁷¹ A. V. Danilova and L. M. Utkin, *Zh. Obshch. Khim.* **30**, 345 (1960) [*CA* **54**, 22698 (1960)].

⁷² A. J. Aasen and C. C. J. Culvenor, *J. Org. Chem.* **34**, 4143 (1969).

⁷³ R. Adams, S. Miyano, and M. D. Nair, *J. Am. Chem. Soc.* **83**, 3323 (1961).

its α' -bromo-D-camphor-*trans*- π -sulfonate salts. The (+)-isomer was identical with macronecine (**115**). Finally, the three other possible racemates with different stereochemistry at C-2 and C-8 were prepared and shown to be different compounds from macronecine by consideration of their NMR spectra.⁷²

A number of closely related naturally occurring pyrrolizidine cyclic ethers have been identified.⁷⁴ Four of these, loline (= festucine⁷⁵) (**119**), norloline (**120**), lolinine (**121**), and decorticasine (**122**), have had their structures and relative configurations established by chemical methods. In addition, the relative stereochemistry of loline has been defined by an X-ray crystal structure determination of its dihydrochloride.⁷⁶ The absolute configurations for all these alkaloid bases have now been established by the X-ray technique of anomalous dispersion using the same dihydrochloride of loline (**119**).⁷⁷



B. PYRROLIZIDINE TRIOLS

There are only two known, naturally occurring trihydric saturated pyrrolizidine bases. The relative stereochemistry of rosmarinine (**123**) was determined by Warren and co-workers.⁷⁸ For the other base, croalbinecine (**124**), the chirality at C-1, C-7, and C-8 was defined by Sawhney *et al.*⁷⁹ by correlation with turnefordine (**113**) as shown in Eq. (33). The location of the third hydroxy group at C-2, indicated by NMR spectroscopy, was confirmed by decoupling experiments. It was further suggested by these workers⁷⁹ that the configuration at C-2 is β -hydroxy, on the basis of the

⁷⁴ Ref. 3, Vol. 8, p. 49.

⁷⁵ A. J. Aasen and C. C. J. Culvenor, *Aust. J. Chem.* **22**, 2021 (1969).

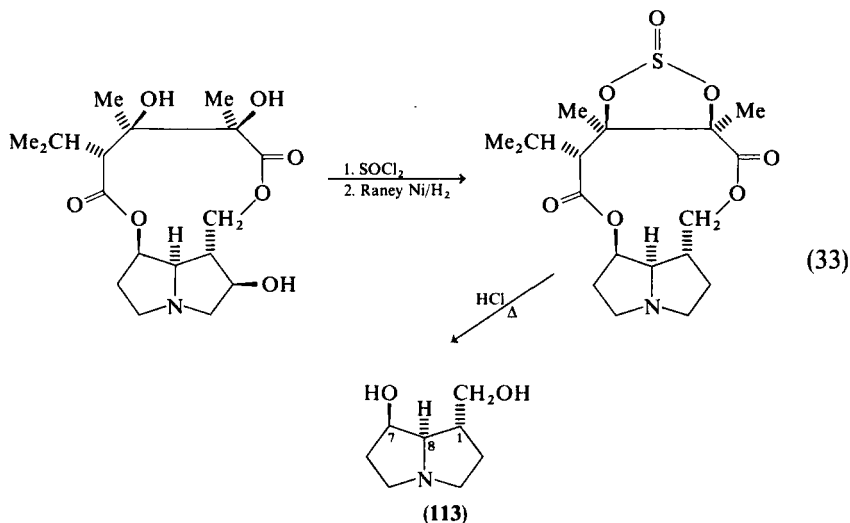
⁷⁶ J. A. S. McMillan, Ph.D. Thesis, University of Illinois, 1964.

⁷⁷ R. B. Bates and S. R. Morehead, *Tetrahedron Lett.*, 1629 (1972).

⁷⁸ L. J. Dry, M. J. Koekemoer, and F. L. Warren, *J. Chem. Soc.*, 59 (1955).

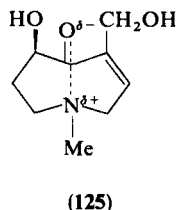
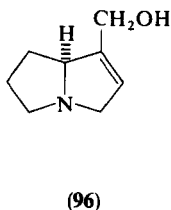
⁷⁹ R. S. Sawhney, C. K. Atal, C. C. J. Culvenor, and L. W. Smith, *Aust. J. Chem.* **27**, 1805 (1974).

magnitude of the coupling constants $J_{1\beta,2}$ and $J_{2,3\beta}$, which are both 8.0 Hz. These are attributed to *trans*-hydrogens in an almost diaxial arrangement, but confirmation of this stereochemistry at C-2 in croalbinecine (**124**) would be desirable.



C. 1,2-DEHYDROPYRROLIZIDINE ALCOHOLS

The absolute configuration of (–)-supinidine (**96**) was established following the degradation of heliotridane (**7**) to *S*-(+)-3-methylheptane⁶⁷ mentioned earlier (Section III,A). More recently, the enantiomeric (+)-supinidine has been isolated by Culvenor and Smith.⁸⁰ This represents the first occurrence of an allylic amino alcohol derived from 8 β -pyrrolizidine.



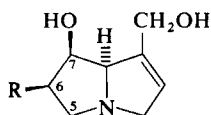
⁸⁰ C. C. J. Culvenor and L. W. Smith, *Aust. J. Chem.* **20**, 2499 (1967).

D. 1,2-DEHYDROPYRROLIZIDINE DIOLS

The structure of otonecine (**125**) was established by degradation.⁸¹ The presence of the transannular system was confirmed by the X-ray studies of Wunderlich on an alkaloid containing otonecine.⁸² This base is found as part of many seco-pyrrolizidine alkaloid structures. The existence of a new alkaloid, isosenkirkine, has been reported in preliminary form.⁸³ It is stated to contain a new transannular base with the opposite chirality to otonecine (**125**) at C-7. No confirmation of this report is yet available.

E. 1,2-DEHYDROPYRROLIZIDINE TRIOLS

The only example of this type of base is crotanecine (**126**), and its structure and stereochemistry were deduced by comparison of its NMR and mass spectra with those of the most widespread pyrrolizidine base, retronecine (**127**).⁸⁴ The magnitude of the vicinal coupling constants of the protons on C-5 of crotanecine (**126**), $J_{5\beta,6} = 9.5$ Hz and $J_{5\alpha,6} = 6.5$ Hz, are consistent with the 6β -hydroxy group and an exo-buckled ring. The other vicinal coupling constants, $J_{6\alpha,7} = J_{7,8} = 3.5$ Hz are indicative of a 7β -hydroxy group, as in retronecine (**127**).



(**126**) R = OH

(**127**) R = H

IV. Spectroscopic Studies

Most of the spectroscopic information available is concerned with the naturally occurring pyrrolizidine alkaloids and their constituent acidic and basic moieties. This material has been well documented,² and new data are

⁸¹ N. I. Koretskaya, A. V. Danilova, and L. M. Utkin, *Khim. Prir. Soedin.*, 22 (1965) [*CA* **63**, 8424 (1965)].

⁸² J. A. Wunderlich, *Chem. Ind. (London)*, 2089 (1962).

⁸³ C. K. Atal and R. S. Sawhney, *Indian J. Pharm.* **35**, 1 (1973).

⁸⁴ C. K. Atal, K. K. Kapur, C. C. J. Culvenor, and L. W. Smith, *Tetrahedron Lett.*, 537 (1966); C. C. J. Culvenor and L. W. Smith, *An. Quim.* **68**, 883 (1972).

reviewed annually.³ Only recent material relating to the pyrrolizidine ring system will be discussed here.

A. UV DATA

Simanek *et al.*⁸⁵ and Gupta *et al.*⁸⁶ have each recorded the UV spectra of about 20 pyrrolizidine derivatives. In the latter study, the UV spectra of platynecine (**43**) and retronecine (**127**) were examined. Platynecine showed three absorption bands in hexane (206.0, 225.6, and 266.9 nm) and only one in methanol (207.0 nm). Retronecine also showed three bands in hexane (206.0, 230.8, and 266.9 nm) and one in methanol (215.0 nm). In methanol, the absorption maximum of retronecine was concentration dependent, varying from 225 to 215 nm as the concentration of the solution was decreased. Gupta *et al.*⁸⁶ attributed this effect to variation in the hydrogen bonding between the solvent and the basic nitrogen. However, it has been suggested that this effect is more likely to be due to decreasing solute-solute interactions on dilution.⁸⁷

B. IR DATA

Gupta *et al.* have also made a compilation of IR data on 25 pyrrolizidine esters.⁸⁸ Peaks at 740–760, 800–950, 960–980, and 1075–1130 cm^{-1} were assigned to ring deformation modes, and absorptions at 610, 750, and 965 cm^{-1} were attributed to the saturated five-membered ring.

Aaron *et al.* have studied the intramolecular hydrogen bonding in hydroxypyrrolizidines.⁸⁹ They found that with 1-hydroxypyrrolizidines, IR spectra did not positively indicate any hydrogen bonding. On the other hand, with 2-hydroxypyrrolizidines, the *cis*-epimer (**128**) is readily isomerized (cyclohexanone, $\text{C}_5\text{H}_{11}\text{OK}/\text{C}_5\text{H}_{11}\text{OH}$) to the more stable *trans*-epimer (**129**), which has a relatively weak intramolecular hydrogen bond, displaying a frequency shift of 35 cm^{-1} [Eq. (34)].

The readily available 3,5-dioxypyrrolizidine (**130**) has been used in several IR studies. Flitsch investigated the IR spectra of a number of azabicyclic diones.⁹⁰ The two imide bands of **130** at 1765 and 1690 cm^{-1} are very

⁸⁵ V. Simanek, A. Klasek, and F. Santavy, *Collect. Czech. Chem. Commun.* **34**, 1832 (1969).

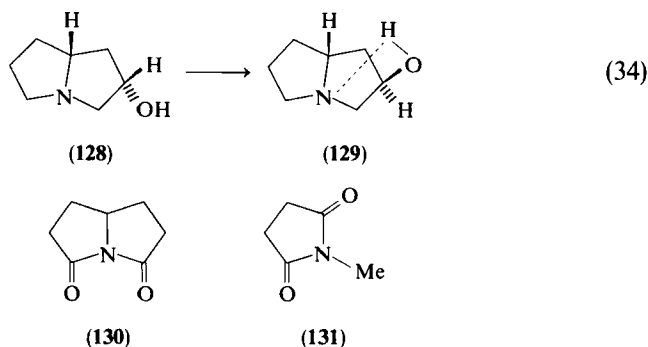
⁸⁶ V. P. Gupta, S. K. Handoo, and R. S. Sawhney, *Indian J. Pure Appl. Phys.* **13**, 776 (1975).

⁸⁷ Ref. 3, Vol. 7, p. 64.

⁸⁸ V. P. Gupta, S. K. Handoo, and R. S. Sawhney, *Curr. Sci.* **44**, 451 (1975).

⁸⁹ H. S. Aaron, C. P. Rader, and G. E. Wicks, *J. Org. Chem.* **31**, 3502 (1966).

⁹⁰ W. Flitsch, *Chem. Ber.* **97**, 1548 (1964).

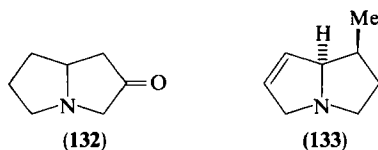


similar to those obtained for the monocyclic compound (131) (1760 and 1690 cm^{-1}). Fayat and Foucaud have estimated the angle between the coupled vibrators (the carbonyl groups) in cyclic imide systems, utilizing the measurement of integrated intensities.⁹¹ With 3,5-dioxopyrrolizidine (130), where the CO-N-CO groups are planar, a satisfactory estimate of the angle between the carbonyl groups of 60° was obtained. The effect of metal ion complexation on this same compound was studied by Mackay and Poziomek.⁹²

C. NMR DATA

Most of the published material is concerned with ^1H -NMR spectra. The use of ^{13}C -NMR has as yet received only sporadic attention.^{3,15} This area is expected to develop rapidly over the next few years.

The ^1H -NMR spectra of pyrrolizidine (1) and its 3-methyl derivatives were obtained over a large temperature range by Skvortsov and Elvidge.⁹³ They verified the general assumption that over the range -70° to $+190^\circ$ pyrrolizidine exists predominantly in the unstrained cis-fused form. Below -60° , the 3-*endo*-methylpyrrolizidine also exists largely in the cis-fused state, but at room temperature the proportion of trans-fused form increases; rapid nitrogen inversion is observed. The same cis-fusion of the two five-membered



⁹¹ C. Fayat and A. Foucaud, *C. R. Acad. Sci., Ser. C* **265**, 345 (1967).

⁹² R. A. Mackay and E. J. Poziomek, *Spectrochim. Acta, Part A* **25**, 283 (1969).

⁹³ I. M. Skvortsov and J. A. Elvidge, *J. Chem. Soc. B*, 1589 (1968).

rings is suggested by Cahill and Crabb for 2-oxopyrrolizidine (**132**) on the basis of the similarity between its NMR spectrum and that of pyrrolizidine.⁹⁴

Culvenor and co-workers have completed a major study of the ¹H-NMR spectra of natural pyrrolizidine bases in the free and esterified states. A detailed analysis was made of the spectra of retronecine (**127**) and its C-7 epimer, heliotridine (**109**).⁹⁵ From consideration of the coupling constants in these two bases, it was concluded that retronecine and its derivatives have an exo-buckled conformation, whereas heliotridine and its derivatives are usually a mixture of rapidly interconverting exo- and endo-buckled conformers of approximately equal populations. This same situation was shown to exist by Pachler *et al.* in their study of heliotridene (**133**).⁹⁶ Furthermore, it was demonstrated that the proportion of endo-buckled form increased to about 75% on acidification.

Several groups of workers have pointed out that in many pyrrolizidine derivatives, H-7 β [as shown in (**109**)] is subject to an unusually large shielding influence because of its position in the fold of the two rings. This shielding applies to pyrrolizidine itself⁹³ and also to 3-oxopyrrolizidine derivatives.⁹⁷ The ¹H-NMR spectra of the fairly rigid, symmetrical 3,5-dioxopyrrolizidine (**130**) has been discussed by Aasen *et al.*⁹⁷ and by Van Binst *et al.*⁹⁸ The latter group of workers obtained the stable conformation by analysis of the 270 MHz NMR spectrum, and the results were correlated with force-field calculations.

D. MASS SPECTROMETRY

The use of mass spectrometry has proved to be extremely helpful in pyrrolizidine alkaloid work for determining the type of base present, and the nature of the esterifying acid(s) when present. The first detailed study was reported by Neuner-Jehle *et al.*⁹⁹ Laburnine (**116**) gives a base peak at *m/e* 83 (**134**) by the usual fragmentation β to the nitrogen. The same base peak has been observed for the isomeric 1-hydroxymethylpyrrolizidines by Abdullaev *et al.*¹⁰⁰ Platynecine (**43**) undergoes similar fission to give ions at

⁹⁴ R. Cahill and T. A. Crabb, *Org. Magn. Reson.* **4**, 259 (1972).

⁹⁵ C. C. J. Culvenor, M. L. Heffernan, and W. G. Woods, *Aust. J. Chem.* **18**, 1605 (1965); C. C. J. Culvenor and W. G. Woods, *Aust. J. Chem.* **18**, 1625 (1965).

⁹⁶ K. G. R. Pachler, J. P. Tollenaere, and P. L. Wessels, *Tetrahedron* **25**, 5255 (1969).

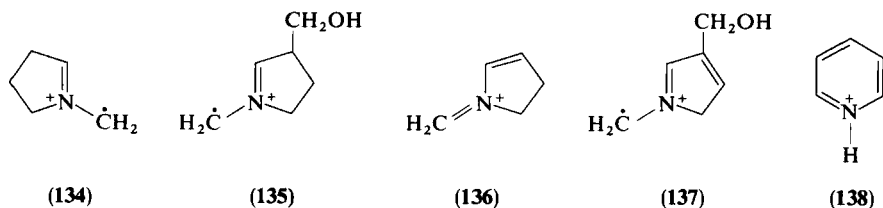
⁹⁷ A. J. Aasen, C. C. J. Culvenor, and R. I. Willing, *Aust. J. Chem.* **24**, 2575 (1971).

⁹⁸ G. Van Binst, Y. Steger, and W. Flitsch, *Z. Naturforsch., Teil B* **30**, 591 (1975).

⁹⁹ N. Neuner-Jehle, H. Nesvadba, and G. Spittler, *Monatsh. Chem.* **96**, 321 (1965).

¹⁰⁰ U. A. Abdullaev, Ya. V. Rashkes, Kh. Shakhidoyatov, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 634 (1972) [*CA* **78**, 84612 (1973)].

m/e 113 (135) and 82 (136). Retronecine (127) fragments to show characteristic ions at m/e 111 (137) and 80 (138). Heliotridine (109) has an identical mass spectrum to retronecine, but these C-7 epimers can be distinguished by measurement of the appearance and ionization potentials.¹⁰¹ All pyrrolizidine alkaloids containing the otonecine nucleus (125) are characterized by fragments at m/e 168, 151, 150, 122, 110, and 94.¹⁰²



The mass spectra of saturated heterocyclic *N*-oxides generally show the presence of the ions M-16, M-17, and M-18.¹⁰³ Abdullaev *et al.* have demonstrated that this holds true for pyrrolizidine bases also.¹⁰⁴ Peaks corresponding to the free bases were also present, together with ions formed by dehydration, dehydrogenation, and isomerization of the nucleus.

E. CHIROPTICAL PROPERTIES

Extensive examinations of the circular dichroism curves of pyrrolizidine alkaloids have been carried out by Culvenor *et al.*¹⁰⁵ and Hrbek *et al.*¹⁰⁶ The free bases tested were divided into four groups, all possessing 8 α -hydrogen atoms. Saturated 1-substituted pyrrolizidines [e.g., 1-methylpyrrolizidine (7) and isoretronecanol (22)] showed negative Cotton effects; while with 1,7-disubstituted pyrrolizidines [e.g., platynecine (43)], the Cotton effects were positive. Dehydropyrrolizidines with 1-substituents [e.g., supinidine (96)] displayed positive Cotton effects, and those with 1,7-disubstitution patterns [e.g., retronecine (127) and heliotridine (109)] exhibited large positive

¹⁰¹ E. Pedersen and E. Larsen, *Org. Mass Spectrom.* **4**, 249 (1970).

¹⁰² M. P. Cava, K. V. Rao, J. A. Weisbach, R. F. Raffauf, and B. Douglas, *J. Org. Chem.* **33**, 3570 (1968); U. A. Abdullaev, Ya. V. Rashkes, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 66 (1976) [*CA* **85**, 177726 (1976)].

¹⁰³ N. Bild and M. Hesse, *Helv. Chim. Acta* **50**, 1885 (1967).

¹⁰⁴ U. A. Abdullaev, Ya. V. Rashkes, and S. Yu. Yunusov, *Khim. Prir. Soedin.*, 620 (1974) [*CA* **82**, 73270 (1975)].

¹⁰⁵ C. C. J. Culvenor, D. H. G. Crout, W. Klyne, W. P. Mose, J. P. Renwick, and P. M. Scopes, *J. Chem. Soc. C*, 3653 (1971).

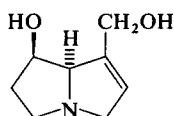
¹⁰⁶ J. Hrbek, L. Hruban, A. Klasek, N. K. Kochetkov, A. M. Likhoshervostov, F. Santavy, and G. Snatzke, *Collect. Czech. Chem. Commun.* **37**, 3918 (1972).

Cotton effects. Otonecine (**125**) does not display the spectral properties of an aminoketone. Circular dichroism effects are absent from otonecine and its derivatives, supporting the zwitterionic representation.¹⁰⁶

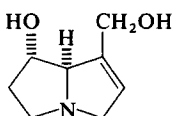
Yamada and Kunieda investigated the application of the octant rule to azabicyclic ketones and found good agreement of the predictions with the experimental results obtained for 1-oxopyrrolizidine of known chirality.¹⁰⁷

F. X-RAY STUDIES

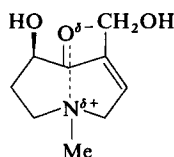
The crystal structures of pyrrolizidine alkaloids that have been determined may be divided into structural groups on the basis of the necine they contain. Alkaloids with retronecine (**127**) as base are fulvine¹⁰⁸ and axillarine,¹⁰⁹ which both have an 11-membered macrocyclic diester ring, and jacobine¹¹⁰ and swazine,¹¹¹ which contain 12-membered diester rings. Heliotrine¹¹² is a C-9 monoester of heliotridine (**109**). Retusamine,¹¹³ clivorine,¹¹⁴ and senkirkine,¹¹⁵ all include otonecine (**125**) as the base portion. The alkaloids



(127)



(109)



(125)

containing retronecine or heliotridine display angles of 115–130° between the two five-membered rings; the largest value is found in heliotridine. A further consequence of the different base is that the saturated five-membered ring in heliotrine is endo-puckered, with a puckering angle of 45°, whereas the four retronecine-based alkaloids exhibit exo-puckering in the pyrrolidine ring, with puckering angles of about 40° (See also Section IV.C). In the otonecine group, the N . . . C=O distance is 1.64 Å in retusamine (the least precise measurement), 2.0 Å in clivorine, and 2.3 Å in senkirkine. It is known that a transannular interaction causes the carbonyl peak in the IR spectrum

¹⁰⁷ S. Yamada and T. Kunieda, *Chem. Pharm. Bull.* **15**, 490 (1967).

¹⁰⁸ J. L. Sussman and S. J. Wodak, *Acta Crystallogr., Sect. B* **29**, 2918 (1973).

¹⁰⁹ H. Stoeckli-Evans and D. H. G. Crout, *Helv. Chim. Acta* **59**, 2168 (1976).

¹¹⁰ J. Fridrichsons, A. M. Mathieson, and D. J. Sutor, *Acta Crystallogr., Sect. B* **16**, 1075 (1963).

¹¹¹ M. Laing and P. Sommerville, *Tetrahedron Lett.*, 5183 (1972).

¹¹² S. J. Wodak, *Acta Crystallogr., Sect. B* **31**, 569 (1975).

¹¹³ J. A. Wunderlich, *Acta Crystallogr.* **23**, 846 (1967).

¹¹⁴ K. B. Birnbaum, *Acta Crystallogr., Sect. B* **28**, 2825 (1972).

¹¹⁵ G. I. Birnbaum, *J. Am. Chem. Soc.* **96**, 6165 (1974).

to shift to a lower frequency.¹¹⁶ It was found that if the N...C=O distances were plotted against the carbonyl frequencies for clivorine, senkirkine, and other compounds that display a similar transannular interaction, a straight line was obtained.¹¹⁵ This may prove to be a useful relationship when more examples are available. The bond orders derived for clivorine and senkirkine across the ring are very small, and the carbonyl bond lengths are close to the normal value for a ketone of 1.215 Å. In both these alkaloids, the plane of the carbonyl group and that containing the double bond of otonecine (125) are inclined at a considerable angle, preventing any effective conjugation.

V. Reactions of Pyrrolizidine and Its Derivatives

A. REACTIONS AT THE PYRROLIZIDINE NITROGEN ATOM

Pyrrolizidines are strong bases and readily form quaternary salts. The formation of these salts has been exploited in a number of syntheses (see Section II,B). Many workers have prepared quaternary pyrrolizidine salts because some exhibit pronounced physiological activity. The most widely investigated compound is diplacin (139), a bisquaternary salt based on platynecine (43).¹ Diplacin possesses strong curarelike activity, and there have been over 50 references to its preparation and use over the past 15 years. Other compounds of this type which display curarelike activity, e.g., 140¹¹⁷ and 141,¹¹⁸ have recently been synthesized by Russian workers. Quaternary pyrrolizidines have also been prepared by allowing naturally occurring alkaloids to react with dihalogen alkanes. These substances possessed neuromuscular blocking activity, and the bromoalkyl pyrrolizidinium bromide (142) was the most potent representative.¹¹⁹

The configurations of the isomeric 3-methylpyrrolizidines have been determined by quaternization experiments.¹²⁰ From models, the endo-isomer (143a) should quaternize readily with alkyl halides, whereas considerable deformation would be required with the exo-form (143b). Using

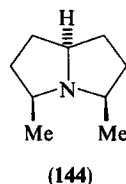
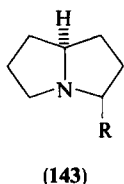
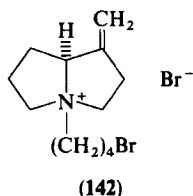
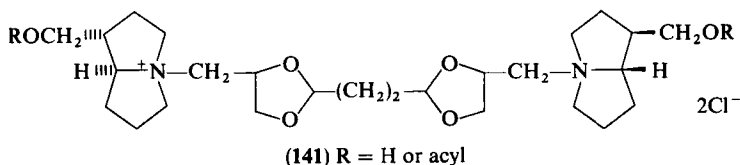
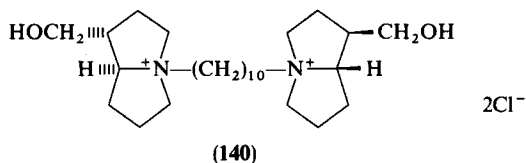
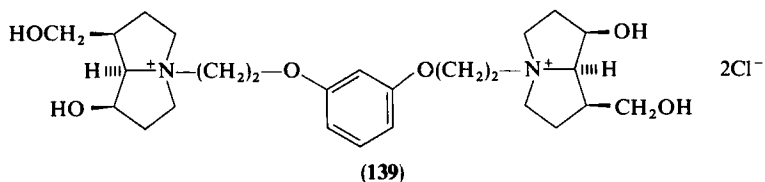
¹¹⁶ F. A. L. Anet and L. Marion, *Can. J. Chem.* **32**, 452 (1954).

¹¹⁷ F. S. Sadritdinov, I. Khamdamov, and B. Rustamov, *Dokl. Akad. Nauk Uzb. SSR* **31**, 22 (1974) [*CA* **84**, 115661 (1976)]; K. M. Shakhidoyatov, N. P. Abdullaev, and C. S. Kadyrov, *Khim. Prir. Soedin.*, 77 (1977) [*CA* **88**, 23214 (1978)].

¹¹⁸ N. P. Abdullaev, K. M. Shakhidoyatov, and C. S. Kadyrov, *Khim. Prir. Soedin.*, 828 (1976) [*CA* **86**, 106446 (1977)].

¹¹⁹ K. A. Suri, R. S. Sawhney, O. P. Gupta, and C. K. Atal, *Indian. J. Pharm.* **38**, 23 (1976); O. P. Gupta, M. M. Ali, B. J. Ghatak, and C. K. Atal, *Indian J. Exp. Biol.* **15**, 220 (1977).

¹²⁰ I. M. Skvortsov, I. V. Antipova, and A. A. Ponomarev, *Dokl. Akad. Nauk SSSR* **178**, 1106 (1968) [*CA* **69**, 67168 (1968)].



a: R = —Me
b: R = |||Me

this theory, the exo- and endo-isomers are easily assigned. In further studies on this theme, the 3,5-dimethylpyrrolizidines were prepared as outlined in Section II,B [Eq. (5)], and the configuration of the isomers was determined by competitive quaternization experiments and spectroscopy.¹²¹ For one of the isomers under investigation (144), it was suggested that the strained trans-form has a relatively high population in the conformational equilibrium.^{121,122} This isomer also readily formed an iminium perchlorate salt,¹²³ supporting the postulated trans-articulated conformation.

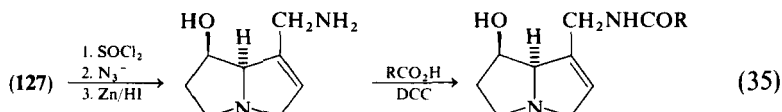
¹²¹ I. M. Skvortsov, I. V. Antipova, G. P. Mal'chenko, and K. V. Ovchinskii, *Vopr. Stereokhim.*, 41 (1974) [*CA* 83, 57923 (1975)]; Y. A. Pentin, I. M. Skvortsov, and I. V. Antipova, *Dokl. Akad. Nauk SSSR* 230, 617 (1976) [*CA* 86, 105764 (1977)].

¹²² I. M. Skvortsov, Y. A. Pentin, T. Xuan-Hoang, I. V. Antipova, and B. I. Drevko, *Khim. Geterotsikl. Soedin.*, 1001 (1976) [*CA* 85, 159250 (1976)].

¹²³ I. M. Skvortsov and A. M. Plotnikov, *Khim. Geterotsikl. Soedin.*, 1003 (1975) [*CA* 83, 178692 (1975)].

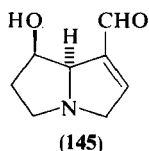
B. REACTIONS OF HYDROXYPYRROLIZIDINES

Many esters, both naturally occurring and semisynthetic, have been prepared by esterification of hydroxy-substituted pyrrolizidine bases. Mattocks synthesized a range of retronecine diesters by heating retronecine (127) hydrochloride with acid chlorides.¹²⁴ Mattocks also converted retronecine into the corresponding amine, retronamine, from which amide analogs of pyrrolizidine esters were prepared¹²⁴ [Eq. (35)].



Hoskins and Crout have synthesized C-9 monoesters of retronecine (127) in reasonable yields by using *N,N'*-dicyclohexylcarbodiimide as the coupling reagent.¹²⁵ The use of *N,N'*-carbonyldiimidazole, with prior formation of the acylimidazole, was necessary with $\alpha\beta$ -unsaturated acids and bulky α -trisubstituted acids. Subsequent esterification at C-7 of the retronecine ester with a suitable acid chloride produced unsymmetrical diesters of retronecine.

Much effort has been expended in developing mild routes for the oxidation of the sensitive allylic alcohols, such as retronecine (127) to the corresponding carbonyl compounds. Mattocks has recently converted retronecine into the aldehyde (145) in 30% yield using specially prepared manganese dioxide under controlled conditions.¹²⁶ This aldehyde (145) is probably an intermediate in the formation of the dihydropyrrolizines (see Section V,D).



C. REACTIONS OF PYRROLIZIDINES CONTAINING AN AMIDE GROUP

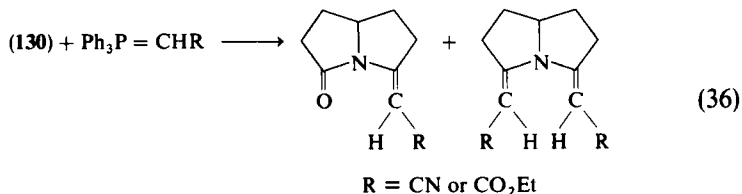
The compound in this category which has been most widely studied is 3,5-dioxypyrrolizidine (130). It shows the typical properties expected of a dilactam structure, and it is a useful intermediate in the preparation of

¹²⁴ A. R. Mattocks, *J. Chem. Soc. C*, 2698 (1969).

¹²⁵ W. M. Hoskins and D. H. G. Crout, *J.C.S. Perkin I*, 538 (1977).

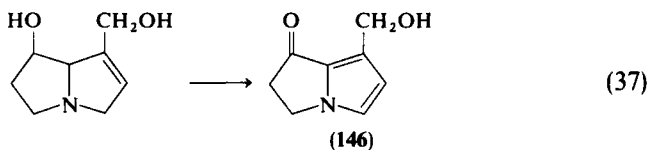
¹²⁶ A. R. Mattocks, *J. Chem. Res. (S)*, 40 (1977).

3,5-disubstituted pyrrolizidines. Flitsch and Mueter have demonstrated that *N*-bridgehead bicyclic imides react in the Wittig process to form mono- and diolefins.¹²⁷ The trans-configuration of the products [Eq. (36)] was elucidated from the NMR spectra.



D. REACTIONS OF UNSATURATED PYRROLIZIDINES

As in the previous review,¹ only reactions of pyrrolizidines with one double bond in the ring will be considered. Interest in dihydropyrrolizine analogs [e.g., (146)] of naturally occurring 1,2-dehydropyrrolizidines is widespread because the dihydropyrrolizines produced in the liver are believed to be the toxic derivatives of the alkaloids. Some of these analogs have potentially useful therapeutic properties, including antitumor, antiviral, and immunosuppressive activity. Consequently, the conversion of the natural dehydropyrrolizidines to the corresponding dihydropyrrolizines under mild conditions has received much attention. Culvenor *et al.*¹²⁸ showed that oxidation of 1,2-dehydropyrrolizidines with 7- and 9-hydroxy substituents took place readily with a suspension of manganese dioxide in chloroform to give 146 and other products [Eq. (37)]. A reductive work up with sodium borohydride was necessary to avoid polymerization. The best method for the production of the dehydro derivatives of the ester alkaloids is by the action of acetic anhydride or ferrous sulfate on the corresponding *N*-oxides.¹²⁹



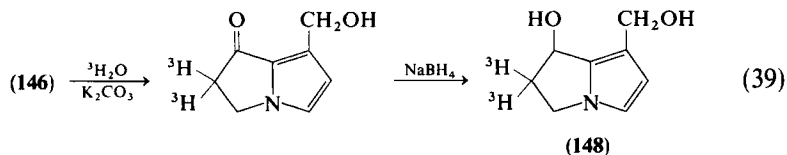
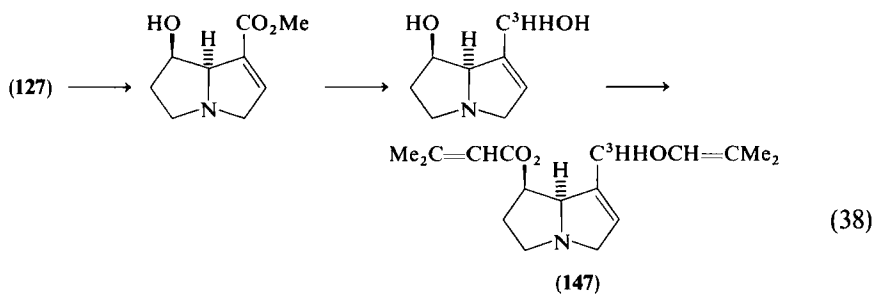
¹²⁷ W. Flitsch and B. Mueter, *Chem. Ber.* **104**, 2852 (1971).

¹²⁸ C. C. J. Culvenor, J. A. Edgar, L. W. Smith, and H. J. Tweeddale, *Tetrahedron Lett.*, 3599 (1969).

¹²⁹ A. R. Mattocks, *J. Chem. Soc. C*, 1155 (1969); C. C. J. Culvenor, J. A. Edgar, L. W. Smith and H. J. Tweeddale, *Aust. J. Chem.* **23**, 1853 (1970); C. C. J. Culvenor, J. A. Edgar, L. W. Smith, and H. J. Tweeddale, *Aust. J. Chem.* **23**, 1869 (1970).

E. RADIOACTIVE LABELING OF PYRROLIZIDINES

Tritium-labeled pyrrolizidine derivatives have been prepared in connection with studies on the biological properties of these molecules. Retronecine (**127**) is the most widespread naturally occurring pyrrolizidine base, and a semisynthetic tritium-labeled pyrrolizidine ester alkaloid was prepared for the investigation of alkaloid toxicity by Hsu and Allen.¹³⁰ Retronecine was oxidized with manganese dioxide in the presence of potassium cyanide and methanol to give the corresponding methyl ester [Eq. (38)]. The label was introduced by reduction of this ester with [³H]lithium aluminum hydride. Acylation with seneciroyl chloride produced the required diseneciroyl retronecine (**147**), which caused cardiopulmonary¹³¹ and hepatic¹³² lesions when injected into rats. Toxicity has been demonstrated in analogs of pyrrolizidine alkaloids with a pyrrole ring. Therefore, tritium-labeled dehydroheliotridine (**148**) was prepared by base-catalyzed exchange of the labile C-6 protons in the ketone (**146**) followed by borohydride reduction¹³³ [Eq. (39)]. The binding of this labeled compound to macromolecules has been studied.^{133,134}



¹³⁰ I. C. Hsu and J. R. Allen, *J. Labelled Compds.* **11**, 71 (1975).

¹³¹ R. C. Schumaker, T. J. Raczniak, W. D. Johnson, and J. R. Allen, *Proc. Soc. Exp. Biol. Med.* **154**, 57 (1977).

¹³² R. C. Schumaker, J. L. Seymour, and J. R. Allen, *Res. Commun. Chem. Pathol. Pharmacol.* **14**, 53 (1976).

¹³³ C. C. Curtain and J. A. Edgar, *Chem.-Biol. Interact.* **13**, 243 (1976).

¹³⁴ R. C. Schumaker, I. C. Hsu, and J. R. Allen, *J. Pathol.* **119**, 21 (1976).

VI. Biogenesis of Naturally Occurring Pyrrolizidines

Robinson's original suggestion¹³⁵ that the natural pyrrolizidine bases are derived *in vivo* from two molecules of ornithine (**149**) has been supported by studies using ¹⁴C-labeled compounds. Ornithine has been shown to be a specific precursor for the pyrrolizidine nucleus present in a variety of alkaloids. The feeding experiments carried out to date are listed in Table I. Three groups of workers have obtained labeled alkaloids after feeding ¹⁴C-labeled ornithines.¹³⁶⁻¹³⁸ Hydrolysis of the alkaloid to yield the free base, retronecine (**127**), has established that almost all the radioactivity is in the base portion. It is likely that ornithine is incorporated into retronecine after decarboxylation to putrescine (**150**) [Eq. (40)] since labeled putrescine is also specifically incorporated into retronecine (Table I).

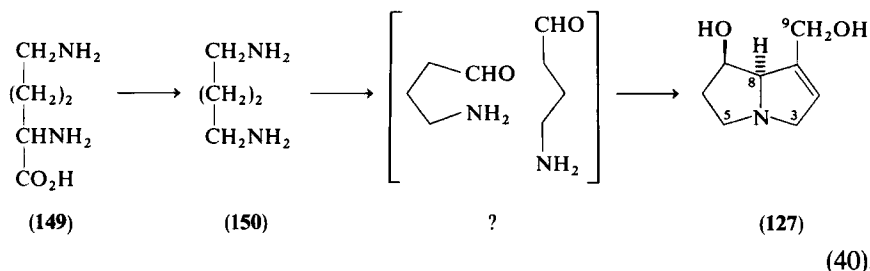


TABLE I
SPECIFIC PRECURSORS OF PYRROLIZIDINES BASES

Plant	Precursor	Alkaloid	Total percent incorporation into alkaloid	Percent activity in retronecine	References
<i>Crotalaria spectabilis</i>	[2- ¹⁴ C]Ornithine	Monocrotaline	0.30	96	136
<i>Senecio isatideus</i>	[5- ¹⁴ C]Ornithine	Retrorsine	0.98	—	137
<i>S. douglasii</i>	[2- ¹⁴ C]Ornithine	Mixture	0.30	94	138
<i>S. douglasii</i>	[5- ¹⁴ C]Ornithine	Mixture	0.75	94	138
<i>S. douglasii</i>	[1,4- ¹⁴ C ₂]Putrescine	Mixture	0.18	98	138

¹³⁵ R. Robinson, in "The Structural Relations of Natural Products," p. 72. Oxford Univ. Press (Clarendon), London and New York, 1955.

¹³⁶ E. Nowacki and R. U. Byerrum, *Life Sci.* **1**, 157 (1962).

¹³⁷ C. A. Hughes, R. Letcher, and F. L. Warren, *J. Chem. Soc.*, 4974 (1964).

¹³⁸ W. Bottomley and T. A. Geissman, *Phytochemistry* **3**, 357 (1964).

Degradations on the alkaloids specifically labeled with ornithine have been carried out and have produced conflicting results. Bottomley and Geissman¹³⁸ degraded the radioactive retronecine obtained from their experiments (Table I). Treatment of retronecine with osmium tetroxide and sodium periodate gave C-9 as the dimedone derivative of formaldehyde. In all three of their experiments (including putrescine as precursor), 25% of the total activity was located at C-2. There are two main conclusions from their work. First, at some stage in the pathway, C-2 and C-5 of ornithine become equivalent (possibly as putrescine), at least in the right-hand side of the retronecine molecule shown in **127**. Second, a symmetrical intermediate may be involved. The assumption is made that 25% of the activity is at C-3, and the remaining 50% is split equally between C-5 and C-8 of retronecine (**127**). However, it should be noted that the location of this remaining 75% of the base activity was not established in any of these experiments. Quite different results were obtained by Hughes *et al.*¹³⁷ from their feeding of [2-¹⁴C]ornithine (Table I). The radioactive base was degraded stepwise by successive Hofmann eliminations. In agreement with the previous results, 26% of the total base activity was found at C-9, but there was no activity at C-5, nor at C-3 [as in (**127**)]. The remainder of the activity (71%) was at C-7 and C-8. The conclusion from their findings is that two molecules of ornithine are incorporated into retronecine in a specific manner involving two different metabolic pools. Clearly, repetition of this labeling work with specifically labeled ornithines, together with complete degradation of the retronecine produced, would be highly desirable to clarify this issue.

Recently, Bale and Crout¹³⁹ have described a double isotope technique for simultaneous measurement of incorporation of two precursors into a natural product. This method was utilized to demonstrate that ornithine is probably a slightly more efficient precursor than arginine for retronecine (**127**) biosynthesis.

ACKNOWLEDGMENTS

The author is indebted to Drs. D. H. G. Crout, R. A. Hill, and J. R. Sweeney for valuable discussions and suggestions.

¹³⁹ N. M. Bale and D. H. G. Crout, *Phytochemistry* **14**, 2617 (1975).

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1,4-Thiazines and Their Dihydro Derivatives

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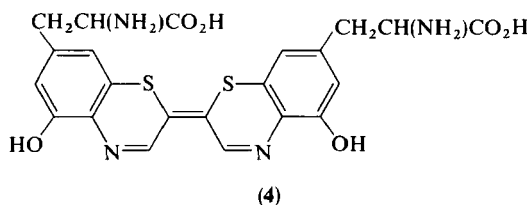
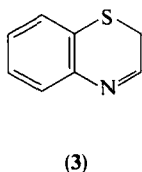
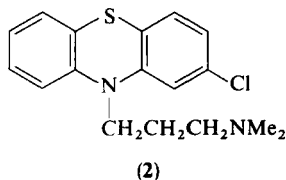
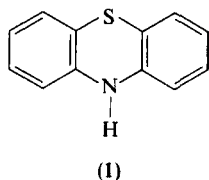
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I. Introduction

Phenothiazine (1), the synthesis of which was reported in 1883 by Bernthsen,¹ was the first 1,4-thiazine derivative to be described. Its chemistry, which has been extensively investigated, has been the subject of both com-

¹ A. Bernthsen, *Ber. Dtsch. Chem. Ges.* **16**, 2896 (1883).

prehensive surveys^{2,3} and short reviews.⁴⁻¹² Derivatives of phenothiazine now play an important role in chemotherapy; for example, chlorpromazine (2) is a valuable antipsychotic agent.



Although an elusive compound because of its high reactivity, 1,4-benzothiazine has recently been prepared and shown to exist as the 2*H*-tautomer 3.¹³ Derivatives of 2*H*-1,4-benzothiazine, however, have been fully studied during the past decade because of their occurrence in trichochromes, pigments that are responsible for the color of feathers and hair; thus trichochrome F, a violet pigment isolated from New Hampshire hens,

² S. P. Massie, *Chem. Rev.* **54**, 797 (1954).

³ C. Bodea and I. Silberg, *Adv. Heterocycl. Chem.* **9**, 321 (1968).

⁴ D. E. Pearson, R. W. Brockman, W. E. Cole, C. M. Greer, and M. V. Sigal, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 6, Ch. 14. Wiley, New York, 1957.

⁵ G. R. Ramage, E. H. Rodd, and J. K. Landquist, in "Chemistry of Carbon Compounds IV^c, Heterocyclic Compounds" (E. H. Rodd, ed.), Ch. XVI. Elsevier, Amsterdam, 1960.

⁶ C. O. Okafor, *Int. J. Sulphur Chem. Part B* **7**, 109 (1972).

⁷ A. V. Kotov and T. M. Zaitseva, *Farmatsiya (Moscow)* **24**, 85 (1975).

⁸ J. Brandt and M. Zarder, *Chem.-Ztg.* **6**, 272 (1975).

⁹ D. H. Reid, in "Organic Compounds of Sulphur, Selenium, and Tellurium" (D. H. Reid, senior reporter), Vol. 1, Ch. 17. Chem. Soc., London, 1970.

¹⁰ G. Protá, in "Organic Compounds of Sulphur, Selenium, and Tellurium" (D. H. Reid, senior reporter), Vol. 2, Ch. 16. Chem. Soc., London, 1973.

¹¹ G. Protá, in "Organic Compounds of Sulphur, Selenium, and Tellurium" (D. H. Reid, senior reporter), Vol. 3, Ch. 16. Chem. Soc., London, 1975.

¹² G. Protá, in "Organic Compounds of Sulphur, Selenium, and Tellurium" (D. R. Hogg, senior reporter), Vol. 4, Ch. 15. Chem. Soc., London, 1977.

¹³ F. Chioccare, E. Novellino, G. Protá, and G. Sodano, *J. Chem. Soc., Chem. Commun.*, 50 (1977).

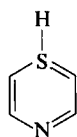
has the structure **4**. The chemistry of 2*H*-1,4-benzothiazines has been reviewed.^{5,9-12,14-16}

Although the subject of brief surveys,^{5,9-12,14} the chemistry of monocyclic 1,4-thiazines has not previously been discussed in a comprehensive manner. The aim of this review is to consider the synthesis, reactivity, and physicochemical properties of these compounds and their dihydro derivatives.

II. 1,4-Thiazines

A. TAUTOMERIC BEHAVIOR

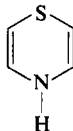
In principle, three tautomeric structures are possible for 1,4-thiazine; these tautomers are 1*H*-1,4-thiazine (**5**), 2*H*-1,4-thiazine (**6**), and 4*H*-1,4-thiazine (**7**).



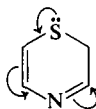
(5)



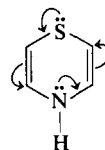
(6)



(7)



(8)



(9)

The parent compound, the first monocyclic 1,4-thiazine to be described, was tentatively assigned the structure **6** on the basis that it failed to form a sulfonamide when subjected to the Hinsberg reaction.¹⁷ Although never confirmed by spectroscopic methods, this formulation is almost certainly correct since several derivatives of 1,4-thiazine have been prepared and shown to exist as the 2*H*-tautomers. This preference suggests that the conjugative stabilization depicted by the process **8** outweighs that illustrated by the process **9**, and that the S-atom does not act as an effective electron sink.

Two derivatives of 4*H*-1,4-thiazine (**7**) are known, but there are no examples of compounds based upon the 1*H*-tautomer **5**.

¹⁴ R. C. Elderfield and E. E. Harris, in "Heterocyclic Compounds" (R. C. Elderfield, ed.), Vol. 6, Ch. 13. Wiley, New York, 1957.

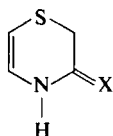
¹⁵ R. H. Thomson, *Angew. Chem., Int. Ed. Engl.* **13**, 305 (1974).

¹⁶ G. Prota and R. H. Thomson, *Endeavour* **35**, 32 (1976).

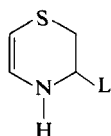
¹⁷ C. Barkenbus and P. S. Landis, *J. Am. Chem. Soc.* **70**, 684 (1948).

B. SYNTHESIS

The available syntheses of 1,4-thiazines utilize dihydrothiazines of types **10** and **11** as precursors.



(10)



(11)

a: L = OH

b: L = H

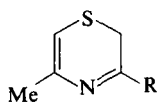
In the former case, the precursors are stable molecules that are readily prepared (Sections V,B and V,C,1,c). The procedure involves the isomerization of the exocyclic double bond at position 3 to an endocyclic location; no change in the oxidation level of the system results. Examples of this type include the conversions of the thiones **12a** and **12b** into the derivatives **13a** and **14** by triethyloxonium tetrafluoroborate and methyl iodide, respectively.¹⁸ A further case, resulting in the formation of the only known monocyclic 4*H*-1,4-thiazine **15**, is provided by the reaction of the thiazinium iodide **14** with potassium *t*-butoxide; the derivative **15** is reported to be an unstable red oil.¹⁸ Although its generality has not been tested, the synthesis



(12)

a: R = H

b: R = Me

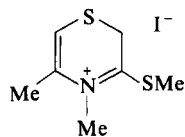


(13)

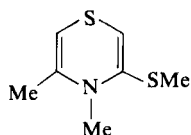
a: R = SEt

b: R = NHC₆H₄Me-*p*

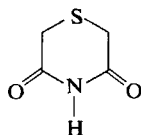
c: R = OH



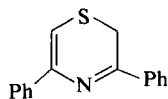
(14)

I⁻

(15)



(16)

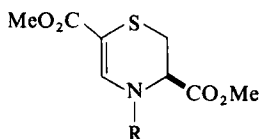


(17)

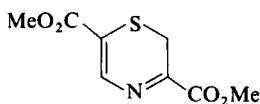
¹⁸ C. R. Johnson and C. B. Thanawalla, *J. Heterocycl. Chem.* **6**, 247 (1969).

is potentially a versatile one, since it may lead to thiazines with different substituents at positions 2, 5, and 6.

The majority of syntheses of 1,4-thiazines involve the elimination of HL from species of type 11. Precursors of type 11a are not usually isolable compounds but are generated as intermediates. Two methods for the formation of such intermediates have been described: one utilizes tetrahydro-1,4-thiazine-3,5-diones as starting materials, and the other requires diacyl sulfides and ammonia. Thus the synthesis of 2*H*-1,4-thiazine (6), reported in 1948, was achieved by heating compound 16 at 450°C in the presence of powdered aluminum.¹⁷ Potentially, the procedure may be applied to the preparation of thiazines variously substituted at positions 2 and 6; however, the low yield (13%) achieved for the parent compound is a detraction. It was initially claimed that the reaction of diphenacyl sulfide with ammonia gave 3,5-diphenyl-4*H*-1,4-thiazine¹⁹; subsequent studies, however, revealed that the product was the 2*H*-tautomer 17.^{20,21} 3,5-Diaryl-2*H*-1,4-thiazines and 3,5-diaryl-2,6-dimethyl-2*H*-1,4-thiazines have also been prepared in good yield by this method, which, in theory, is the most versatile so far available^{21,22}; it may lead to the derivation of thiazines containing different substituents at positions 2, 3, 5, and 6. Attempts to prepare 4-substituted

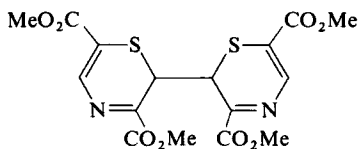


(18)



(19)

- a: R = H
b: R = NO
c: R = Me
d: R = COMe



(20)

¹⁹ K. Fujii, *Yakugaku Zasshi* **77**, 359 (1957) [*CA* **51**, 12103 (1957)].

²⁰ C. R. Johnson and I. Sataty, *J. Med. Chem.* **10**, 591 (1967).

²¹ D. Sica, L. Paolillo, and J. A. Ferretti, *Ric. Sci.* **37**, 629 (1967); D. Sica, C. Santacroce, and R. A. Nicolaus, *Gazz. Chim. Ital.* **98**, 17 (1968).

²² D. Sica, *Corsi Semin. Chim.* **11**, 104 (1968).

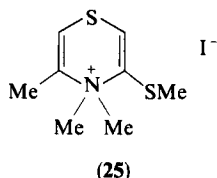
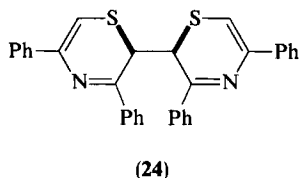
is the precursor of the product; the ensuing autoxidation, for which there is precedent (Section V,C,1,c), is presumably facilitated by the generation of the extensively conjugated system.

C. REACTIVITY

1. Retention of the Thiazine Ring

2*H*-1,4-Thiazines, unsubstituted at position 2, readily undergo oxidative coupling reactions. Thus, in ethanol containing picric acid, the thiazine **17** was converted into the bis(thiazine) **24** in good yield.²⁶ The oxidative dimerization was also induced, albeit in lower yield, by nitrobenzene at 140°C and by 2,3-dichloro-5,6-dicyano-1,4-benzoquinone at ambient temperature. Only one diastereoisomer, shown to be the meso derivative, was produced in each case. An analogous autoxidation, to give the bis(thiazine) **20**, as a single isomer in 39% yield, occurred when the thiazine **19** was heated in toluene under oxygen.²⁴

Only one reaction involving the substituent at position 3 has been described. Thus, when treated with *p*-aminotoluene under acidic conditions, the thiazine **13a** was converted into the derivative **13b**.¹⁸ Attempts to replace the ethylthio moiety of compound **13a** with an alkyl group, by employing a Grignard reagent, were unsuccessful.¹⁸



2*H*-1,4-Thiazines are weak bases (Section II,D,5), and the parent compound is reported to form salts with picric acid, chloroplatinic acid, and hydrogen chloride.¹⁷ Alkylation, to give the thiazinium iodide **25**, occurred when the thiazine **15** was treated with methyl iodide¹⁸; the derivative **25** is the only known example of a 4*H*-1,4-thiazinium salt.

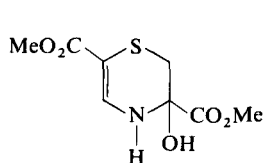
2. Loss of the Thiazine Ring

a. No Change of the Ring Skeleton

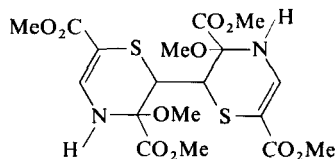
In principle, additions may occur to the double bonds of thiazines. A few examples of such reactions, involving the C=N bonds of 2*H*-1,4-thiazines,

²⁶ D. Sica, G. Santacroce, and G. Protta, *J. Heterocycl. Chem.* **7**, 1143 (1970).

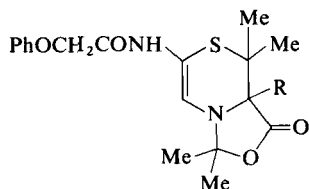
are known. Thus the thiazine **19** was converted into the dihydrothiazine **26**, when treated with dilute hydrochloric acid²³; similarly, the bis(thiazine) **20** afforded the compound **27**, as a single diastereoisomer, in the presence of methanolic hydrogen chloride.²⁴ As already mentioned (Section II,B), dihydrothiazines of type **11a** are usually not isolable compounds; the stability of the derivatives **26** and **27** is presumably associated with the presence of the vinylogous urethan moiety.



(26)



(27)



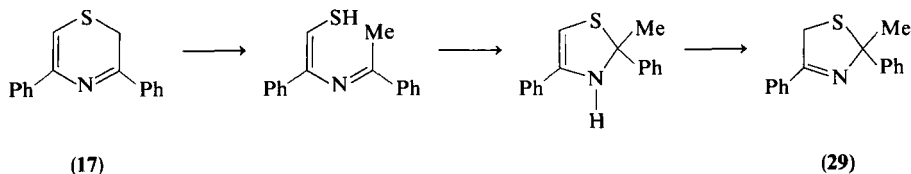
(28)

- a: R = CH₂Cl
b: R = PO(OEt)₂

The C=N bond of 2*H*-1,4-thiazinium salts is expected to be particularly susceptible to attack by nucleophilic reagents. Two examples involving the compound **23** are known; thus, with diazomethane and triethyl phosphite, the thiazinium chloride **23** afforded the derivatives **28a** and **28b**, respectively.²⁵

b. Change of the Ring Skeleton

It was originally claimed that the thiazine **17** was converted into its tetrahydro derivative when hydrogenated over platinum oxide.¹⁹ Subsequent

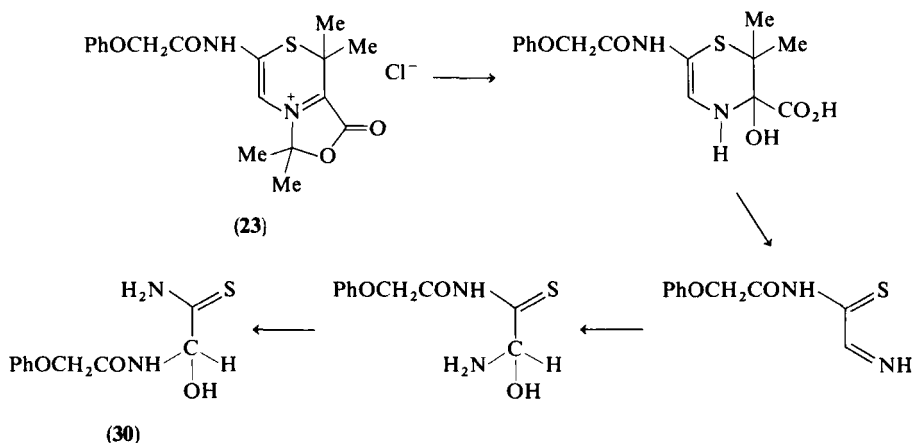


SCHEME 2

investigations, however, revealed that the product was the thiazoline **29**^{21,22}; the hydrogenolysis probably occurred by the route of Scheme 2.

c. Rupture of the Ring Skeleton

In principle, acidic hydrolysis of a 1,4-thiazine may lead to the formation of ammonia and a dicarbonyl compound. In the case of 3,5-diaryl-2*H*-1,4-thiazines, this hydrolysis occurred under very mild conditions; thus the thiazine **17** was converted into ammonia and diphenacyl sulfide by dilute hydrochloric acid at ambient temperature.²¹ In aqueous acetone at pH 7, the thiazinium chloride **23** underwent an interesting hydrolytic cleavage to give the thioamide **30**²⁵; a possible reaction pathway is suggested in Scheme 3.



SCHEME 3

D. PHYSICOCHEMICAL PROPERTIES

1. Infrared Spectra

Compelling evidence that *N*-unsubstituted 1,4-thiazines exist as the 2*H*-tautomers is provided by IR spectroscopy^{18,20,21,23,24}; thus, the derivatives **13a**, **17**, **19**, **20**, and **24** show no absorptions in the region characteristic of N-H stretching vibrations. Bands attributable to C=N and C=C stretching vibrations are observed in the 1550–1640 cm⁻¹ region. Usually two bands, of medium to strong intensity, are discernible; for example, the thiazine **17** absorbs at 1573 and 1600 cm⁻¹. The C=O stretching vibrations

of compounds **19** and **20** appear in the $1715\text{--}1725\text{ cm}^{-1}$ region, a frequency range in which α,β -unsaturated carboxylic esters typically absorb.²⁷

2. Ultraviolet Spectra

Although 2*H*-1,4-thiazine (**6**) is reported to be a colorless liquid, most of its derivatives are yellow.

The paucity of examples^{18,21,22} allows for only a brief discussion of the UV spectra of 2*H*-1,4-thiazines. In principle, such compounds are expected to display $n \rightarrow \pi^*$ transitions for the $\text{S}=\text{C}=\text{C}-\text{N}=\text{C}$ chromophore. The absorptions at 336 and 360 nm of the derivatives **13a** and **19** and in the 370–385 nm region of 3,5-diaryl-2*H*-1,4-thiazines are possibly due to these transitions; in general, their molar extinction coefficients are of moderate intensity (ϵ 1250–6750). Other absorptions, at 251 and 300 nm in the case of the compounds **13a** and **19** and in the 261–274 nm region for 3,5-diaryl-2*H*-1,4-thiazines, are also observed; the last-mentioned bands are of high intensity (ϵ 26,900–44,700) and are presumably caused by excitations involving the aryl groups.

3. Nuclear Magnetic Resonance Spectra

The protons at position 2 of 2-unsubstituted 2*H*-1,4-thiazines resonate in the δ 3.36–3.40 region.^{21–23} The chemical shift of the 3-proton of a 3-unsubstituted 2*H*-1,4-thiazine has not been reported, and the only example of a 5-unsubstituted 2*H*-1,4-thiazine whose NMR spectrum is available is compound **19**; its 5-proton absorbs at δ 8.43.²³ The 6-protons of 3,5-diaryl-2*H*-1,4-thiazines appear in the δ 6.30–6.53 region^{21,22}; a slight deshielding of the 6-proton (to δ 6.13) is observed in the case of the bis(thiazine) **24**.

2,6-Unsubstituted 2*H*-1,4-thiazines display long-range coupling ($J = 1.0\text{--}1.3\text{ Hz}$) between the 2- and 6-protons.^{21,22}

4. Crystal Structure

There are two reports of X-ray diffraction studies involving 1,4-thiazines. Thus the meso configuration of the bis(thiazine) **24** was established by the observation that the molecule possessed a center of symmetry.²⁶ The crystal structure of the thiazinium chloride **23** has also been described²⁵; however,

²⁷ L. J. Bellamy, in "The IR Spectra of Complex Molecules," pp. 181–182. Wiley, New York, 1958.

few data were included in the communication except that the S1—C6 bond (172.8 pm) was short compared with the S1—C2 bond (185.4 pm), a result in accord with a significant degree of π -bonding between the sulfur atom and the C=C bond.

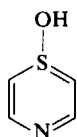
5. Basicity

The parent compound **6** is the only 1,4-thiazine whose base strength has been determined.¹⁷ It possesses a pK_a of 5.6, comparable to pyridine (pK_a 5.2).

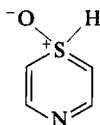
III. 1,4-Thiazine 1-Oxides

A. TAUTOMERIC BEHAVIOR

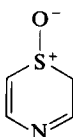
In principle, 1,4-thiazine 1-oxide may exist as one of the four tautomeric structures **31**–**34**. Only derivatives of 1*H*-1,4-thiazine 1-oxide (**32**) have so far been reported.



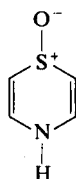
(31)



(32)



(33)



(34)

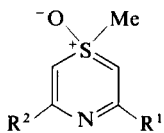
B. SYNTHESIS

There is only one report of an attempt to prepare a thiazine oxide of type **33** or **34**; however, the reaction of diphenacyl sulfoxide with ammonia afforded an intractable product.²⁰ Surprisingly, no attempts appear to have been made to oxidize thiazines at position 1.

It was suggested in 1958 that the minor product obtained from the reaction of dimethylsulfoxonium methylide with benzonitrile possessed the structure **35a**.²⁸ Recently, related compounds **35b** and **35c** have been prepared by the reaction of the ylide with the cyanamide derivatives **36a** and **36b**.²⁹ The structures of the thiazine oxides **35** were assigned on the basis of their spectroscopic properties (Section III,D); in the case of the compound **35a**,

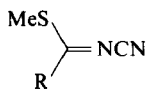
²⁸ H. König, H. Metzger, and K. Seelert, *Chem. Ber.* **98**, 3724 (1965).

the alternative structure **37** was rendered unlikely by its lack of reactivity with peracetic acid.²⁸



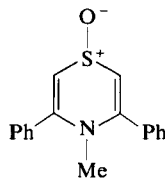
(35)

- a: $R^1 = R^2 = \text{Ph}$
 b: $R^1 = \text{NH}_2$; $R^2 = \text{SMe}$
 c: $R^1 = \text{NH}_2$; $R^2 = \text{OMe}$



(36)

- a: $R = \text{SMe}$
 b: $R = \text{OMe}$



(37)

C. REACTIVITY

There is virtually no information on the reactivity of the derivatives **35**; only trivial reactions, involving the acetylation of the amino groups of compounds **35b** and **35c** with acetic anhydride, have been reported.²⁹

D. PHYSICOCHEMICAL PROPERTIES

1. Infrared Spectra

Compound **35c** is reported to show $\text{C}=\text{C}$ and S^+-O^- stretching vibrations at 1522 and 1063 cm^{-1} , respectively²⁸; sulfoxides usually display a strong absorption in the $1045\text{--}1060\text{ cm}^{-1}$ region.³⁰

2. Nuclear Magnetic Resonance Spectra

The ring protons of compound **35a** resonate at $\delta\ 6.30$ ²⁸ whereas those of the derivative **35b** appear at $\delta\ 4.68$ and 5.42 ²⁹; long-range coupling ($J = 4\text{ Hz}$) is observed between the latter protons.

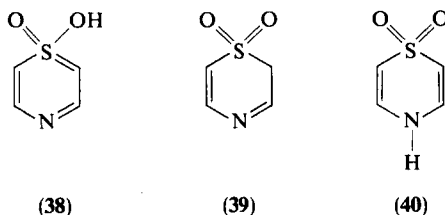
²⁹ M. Watanabe, M. Minohara, K. Masuda, T. Kinoshita, and S. Furukawa, *Heterocycles* **4**, 1875 (1976).

³⁰ D. Barnard, J. M. Fabian, and H. P. Koch, *J. Chem. Soc.*, 2442 (1949).

IV. 1,4-Thiazine 1,1-Dioxides

A. TAUTOMERIC BEHAVIOR

Three tautomeric structures **38**–**40** are possible for 1,4-thiazine 1,1-dioxide.



On the basis of spectroscopic evidence (Section IV.D), it is clear that the parent compound and its derivatives exist as the *4H*-tautomers, viz. **40**; this preference is presumably due to the conjugative stabilization associated with the vinylogous sulfonamide moiety. Derivatives of the tautomers **38** and **39** have not been described.

B. SYNTHESIS

There are two basic methods for the formation of 1,4-thiazine 1,1-dioxides. They rely upon the generation of intermediates of types **41** and **42**, which spontaneously eliminate water, hydrogen chloride, or carbon dioxide.

Two procedures for the generation of intermediates of type **41a** are available: one utilizes diacyl sulfones and ammonia as starting materials^{19,20,31–34}; and the other, dimethyl sulfone, sodium amide, and nitriles.³⁵ For example, by using the former method, the thiazine dioxides **40** and **43a** were obtained in good yield; although attempts to replace ammonia by methylamine and ethylamine were unrewarding,³¹ benzylamine did react with diphenacyl sulfone to give a low yield of compound **43b**.²⁰ In principle, the foregoing procedure is a versatile one and may lead to thiazine dioxides differentially substituted at positions 2, 3, 5, and 6. When the disodium salt of dimethyl sulfone was heated with benzonitrile and the mixture acidified,

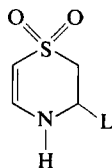
³¹ V. Baliah and T. Rangarajan, *J. Org. Chem.* **26**, 970 (1961).

³² G. Pagani and S. Maiorana, *Chim. Ind. (Milan)* **49**, 1194 (1967).

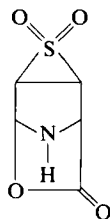
³³ M. I. Ali, A. F. Dawsoud, and A. A. Soliman, *J. Prakt. Chem.* **318**, 865 (1976).

³⁴ W. E. Noland and R. D. DeMaster, in "Organic Syntheses" (H. O. House, ed.), Vol. 52, p. 135. Wiley, New York, 1972.

³⁵ E. M. Kaiser, R. D. Beard, and C. R. Hauser, *J. Organomet. Chem.* **59**, 53 (1973).



(41)



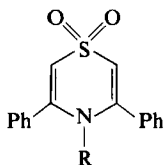
(42)

a: L = OH

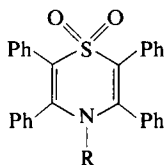
b: L = Cl

compound **43a** was obtained in low yield. The generality of this synthesis, which may be adapted to afford thiazine dioxides symmetrically substituted at positions 3 and 5, has not been examined.

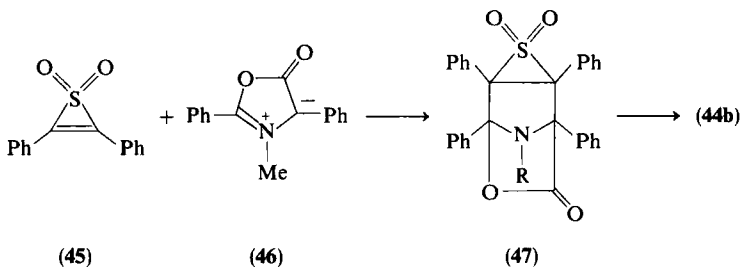
An intermediate of type **41b** is probably involved in the formation of compound **44a** from the reaction of bis(2-chloro-1,2-diphenylvinyl) sulfone with sodamide³⁶; the sulfone was prepared by the addition of sulfur dichloride to diphenylacetylene followed by oxidation of the adduct with hydrogen peroxide.



(43)

a: R = H
b: R = CH₂Ph
c: R = Me

(44)

a: R = H
b: R = Me

(45)

(46)

(47)

a: R = Me

b: R = H

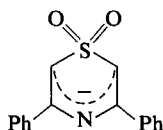
³⁶ W. Ried and W. Ochs, *Synthesis*, 311 (1972).

Intermediates of type **42** may be generated by cycloaddition reactions.³⁷ Thus, when the thiirene 1,1-dioxide **45** was treated with the mesoionic compound **46** at ambient temperature, the sulfone **44b** was produced in high yield; the thiazine dioxide **44a** was prepared in a similar manner. It is noteworthy that the intermediate cycloadducts **47a** and **47b** lost carbon dioxide in preference to sulfur dioxide.

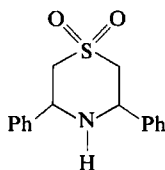
C. REACTIVITY

1. Retention of the Thiazine Dioxide Ring

When heated with methyl iodide and potassium carbonate, the sulfone **43a** was converted into the *N*-methyl derivative **43c** in good yield^{20,31}; corresponding alkylations were achieved with other primary halides.²⁰



(48)



(49)

The anion **48**, the species involved in the foregoing alkylations, was quantitatively generated by the addition of potassium *t*-butoxide to the sulfone **43a** dissolved in [²H₆]dimethyl sulfoxide.³⁸ In accord with its delocalized structure, the anion **48** underwent hydrogen–deuterium exchange at positions 2 and 6.

2. Loss of the Thiazine Dioxide Ring

a. No Change of the Ring Skeleton

Compound **43a** was reduced at the C=C bonds to the tetrahydrothiazine dioxide **49**, by either hydrogen over platinum oxide¹⁹ or lithium aluminium hydride.²⁰

b. Change of the Ring Skeleton

When heated, thiazine dioxides are reported to lose sulfur dioxide and to afford pyrroles^{32,36}; for example, 2,5-diphenylpyrrole is formed when compound **43a** is heated at 300°C over copper.

³⁷ H. Matsukubo, M. Kojima, and H. Kato, *Chem. Lett.*, 1153 (1975).

³⁸ I. Sataty, *J. Org. Chem.* **34**, 250 (1969).

D. PHYSICOCHEMICAL PROPERTIES

1. *Infrared Spectra*

Persuasive evidence that *N*-unsubstituted thiazine dioxides exist as the 4*H*-tautomers is provided by IR spectroscopy^{20,34-36}; thus the compounds **40**, **43a**, and **44a** show absorptions in the 3360–3380 cm⁻¹ region, attributable to N—H stretching vibrations. Bands ascribable to C=C stretching vibrations are observed in the 1675–1645 cm⁻¹ region. The symmetrical and asymmetrical stretches of the sulfone group typically cause strong absorptions at 1130–1160 and 1310–1335 cm⁻¹, respectively.³⁰ In the case of thiazine dioxides, such absorptions occur in the 1105–1135 and 1280–1295 cm⁻¹ regions.

2. *Ultraviolet Spectra*

Only the UV spectrum of the parent compound **40** has been described³⁴; it displays absorption maxima at 226 nm (ϵ 8800), 277 nm (ϵ 7200), and 287 nm (ϵ 7400). Presumably, the 277 and 287 nm bands are associated with $n \rightarrow \pi^*$ transitions of the $\ddot{\text{N}}-\text{C}=\text{C}-\text{SO}_2$ chromophore.

3. *Nuclear Magnetic Resonance Spectra*

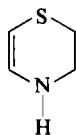
The protons at positions 2 and 6 of symmetrical thiazine dioxides resonate in the δ 5.95–6.36 region^{20,34,35,38}; in the case of the anion **48**, the protons are shifted upfield by 0.45 ppm (to δ 5.91).³⁸ The parent compound **40** provides the only example of a 4*H*-1,4-thiazine dioxide, unsubstituted at positions 3 and 5, whose NMR spectrum has been reported; the 3- and 5-protons appear as a multiplet centered at δ 7.06.³⁴

V. Dihydro-1,4-thiazines

A. TAUTOMERIC BEHAVIOR

Two tautomeric structures are possible for dihydro-1,4-thiazine; these tautomers are 3,4-dihydro-2*H*-1,4-thiazine (**50**) and 5,6-dihydro-2*H*-1,4-thiazine (**51**).

Although the parent compound has not been described, several of its derivatives have been prepared; in general, they exist as the 3,4-dihydro tautomers. Derivatives of the 5,6-dihydro compound **51** are also known; they are normally obtained when the 2-position is disubstituted.



(50)



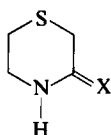
(51)

B. SYNTHESIS

It is appropriate to classify the syntheses into four broad types, which reflect the nature of the immediate precursor of the dihydrothiazine ring.

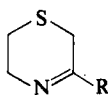
1. Isomerization of Tetrahydrothiazines

This method depends on the isomerization of the exocyclic double bond at position 3 of a compound of type **52** to an endocyclic position.



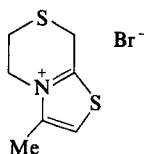
(52)

a: X = O
b: X = S
c: X = NH

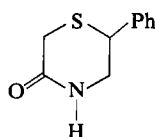


(53)

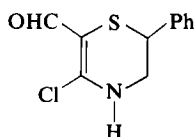
a: R = OEt
b: R = NH₂



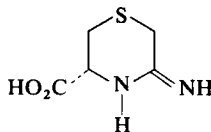
(54)



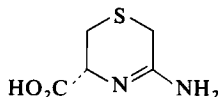
(55)



(56)



(57)



(58)

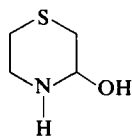
Usually, precursors of type **52** are stable, readily prepared compounds. Thus the derivative **52a** was converted into the dihydrothiazine **53a** when

treated with triethyloxonium tetrafluoroborate³⁹; stabilization by the imino ether moiety is presumably responsible for the preference of the 5,6-dihydro tautomer. Similarly, the thione **52b**, prepared by treating compound **52a** with phosphorus pentasulfide, was transformed into the dihydrothiazinium salt **54** with 1-bromopropan-2-one⁴⁰; in this instance, the preference for the 5,6-dihydro tautomer is clearly due to the aromatic stabilization of the thiazolium ring. A further example is provided by the reaction of the tetrahydrothiazinone **55** with phosphorus oxychloride and *N,N*-dimethylformamide (the Vilsmeier–Haack reagent) to give **56**.⁴¹

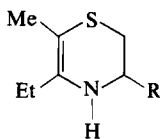
Compounds of type **52** or **53** may also be generated from acyclic precursors; in these instances, the preferred tautomer is unestablished. Thus the reaction of β -mercaptoethylamine with chloroacetonitrile afforded a product that possessed either the structure **52c** or **53b**.⁴² A similar reaction occurred with L-cysteine and chloroacetonitrile; in this case, the product existed as a zwitterion of the species **57** or **58**.⁴³

2. Dehydration of Tetrahydrothiazinols

In general, species of type **59** spontaneously eliminate water. There are several syntheses of dihydrothiazines that depend upon this process; they will be classified according to the nature of the starting materials that are used to generate the precursors.

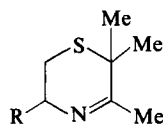


(59)



(60)

a: R = H
b: R = Me



(61)

a: R = H
b: R = Me

³⁹ R. G. Glushkov and A. R. Todd, *Khim. Geterotsikl. Soedin.*, 433 (1968) [*CA* **69**, 106668 (1968)].

⁴⁰ V. P. Khilya, C. P. Kutrov, and F. S. Babichev, *Khim. Geterotsikl. Soedin.*, 1043 (1967) [*CA* **70**, 12646 (1969)].

⁴¹ O. Aki and Y. Nakagawa, *Chem. Pharm. Bull.* **20**, 1325 (1972); *Japan Kokai* 73, 22476 (1973) [*CA* **79**, 18735 (1973)].

⁴² L. Goodman, L. O. Ross, and B. R. Baker, *J. Org. Chem.* **23**, 1954 (1958).

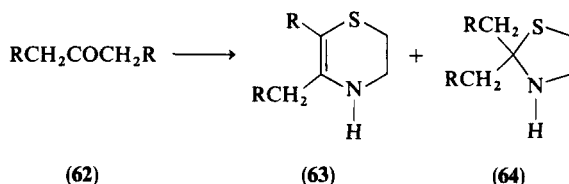
⁴³ L. Goodman, L. O. Ross, and B. R. Baker, *J. Org. Chem.*, **23**, 1251 (1958).

a. α -Mercapto Ketones and Aziridines

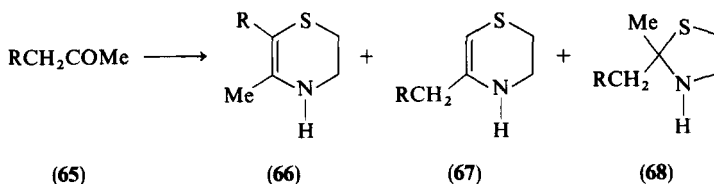
The reactions of α -mercapto ketones with aziridines have been used to prepare derivatives of the dihydrothiazines **50** and **51**⁴⁴⁻⁴⁷; for example, 2-mercaptopentan-3-one and 3-mercapto-3-methylbutan-2-one afforded the compounds **60a** and **61a** with aziridine, and the derivatives **60b** and **61b** with 2-methylaziridine. In general, good yields of dihydrothiazines are obtained by this route.

b. Sulfur, Aldehydes or Ketones, and Aziridine

Dihydrothiazines may be prepared by the action of elemental sulfur and aziridine upon ketones⁴⁸⁻⁵⁰; the outcome of the reaction is markedly dependent upon the structure of the ketone. Thus with symmetrical ketones of type **62**, e.g., pentan-3-one, heptan-4-one, cyclopentanone, cyclohexanone, and cyclooctanone, dihydrothiazines of type **63** were obtained in high yields; symmetrical thiazolidines of type **64** were also formed as minor by-products.



In principle, the reactions of unsymmetrical ketones of type **65** with sulfur and aziridine may lead to the products **66**, **67**, and **68**; usually all three compounds are formed, although dihydrothiazines of type **66** predominate.



⁴⁴ F. Asinger, F. J. Schmitz, and S. Reichel, *Justus Liebigs Ann. Chem.* **652**, 50 (1962).

⁴⁵ S. Rossi, T. Bachetti, and S. Maiorana, *Gazz. Chim. Ital.* **92**, 1367 (1962).

⁴⁶ F. Asinger, H. Diem, and W. Schäfer, *Monatsh. Chem.* **95**, 1335 (1964).

⁴⁷ A. K. Bose, V. Sudarsanam, B. Anjaneyula, and M. S. Manhas, *Tetrahedron* **25**, 1191 (1969).

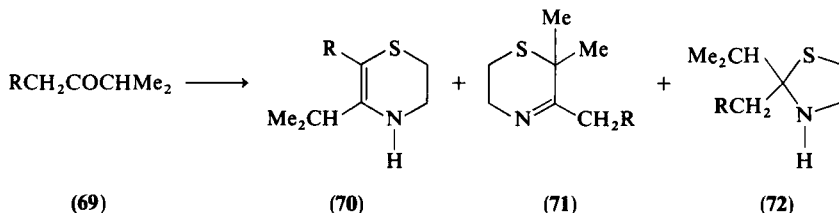
⁴⁸ F. Asinger, H. Offermanas, W. Pürschel, K. H. Lim, and D. Neuray, *Monatsh. Chem.* **99**, 2090 (1968).

⁴⁹ F. Asinger, H. Offermanns, K. H. Lim, and D. Neuray, *Monatsh. Chem.* **101**, 1281 (1970).

⁵⁰ F. Asinger, A. Saus, H. Offermanns, D. Neuray, and K. H. Lim, *Monatsh. Chem.* **102**, 321 (1971).

For example, butan-2-one (**65**; R=Me) afforded a 75:8:17 mixture of the materials **66** (R=Me), **67** (R=Me), and **68** (R=Me) in 60% yield.

Unsymmetrical ketones of types **69** may react with sulfur and aziridine to give dihydrothiazines **70** and **71** and thiazolidines **72**; although all three compounds are formed, there is a marked preference for the derivative **70**. Thus with 2-methylpentan-3-one (**69**; R=Me), a 78:2:20 mixture of the compounds **70** (R=Me), **71** (R=Me), and **72** (R=Me) was isolated in 54% yield.



Although the precise pathway involved in the aforementioned synthesis has not been established, it is clear that 3,4-dihydro-2H-1,4-thiazines are formed in preference to thiazolidines, which, in turn, are preferred to 5,6-dihydro-2H-1,4-thiazines. The dihydrothiazines are probably produced from α -mercaptoketones, formed by the action of elemental sulfur upon the ketones, and aziridine. It seems likely that the thiazolidines arise from the reactions of the ketones with β -mercaptoethylamine, produced from aziridine and hydrogen sulfide; a competing reaction of the α -mercaptoketone with sulfur is probably responsible for the generation of hydrogen sulfide.

Attempts to utilize aldehydes in place of ketones in the foregoing reactions have met with limited success.⁵¹ Thus propanal, in the presence of *N,N*-dimethylformamide or potassium carbonate, reacted with sulfur and aziridine to give a 1.3:1 mixture of 3,4-dihydro-6-methyl-2H-1,4-thiazine and 2-ethylthiazolidine in 23% yield. Although somewhat better yields were achieved by using butanal and pentanal, the thiazolidines were then the predominant products.

c. β -Mercaptoethylamines and α -Haloketones

The reactions of β -mercaptoethylamine, L-cysteine, and D-penicillamine, and their derivatives, with α -haloketones represent an important synthetic route to dihydrothiazines.^{44-46,52-54} For example, the methyl esters of L-cysteine and D-penicillamine reacted with 3-bromo-2-oxopropionic acid

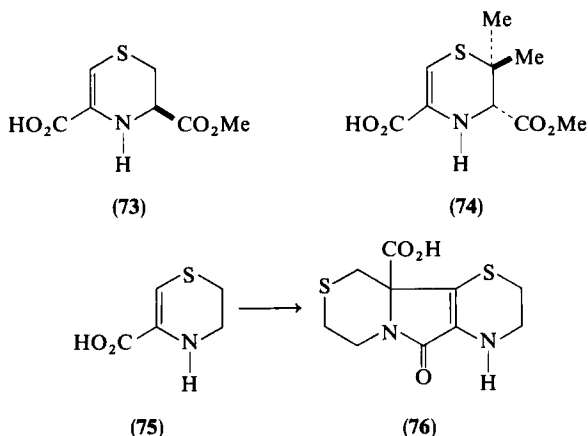
⁵¹ F. Asinger, H. Offermanns, D. Neuray, and P. Müller, *Monatsh. Chem.* **101**, 1295 (1970).

⁵² I. T. Strukov, *Zh. Obshch. Khim.* **28**, 69 (1958) [*CA* **52**, 12848 (1958)].

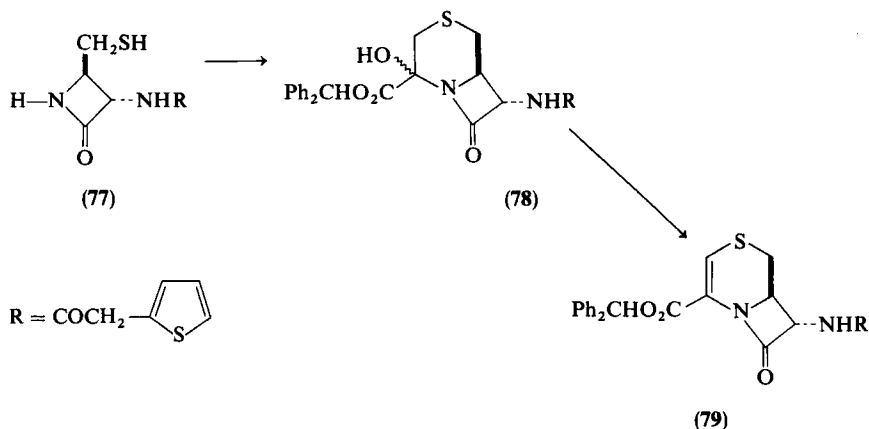
⁵³ P. Hermann, *Chem. Ber.* **94**, 442 (1961).

⁵⁴ S. S. Husain and G. Lowe, *Chem. Commun.*, 344 (1965).

to give the compounds **73** and **74**.⁵² The corresponding reaction of β -mercaptoethylamine, however, did not yield the expected material **75**; instead, an acidic product, which was tentatively considered to possess the structure **76**, was isolated.⁵³ The acid **76** was presumably formed by a dimerization and dehydration of the dihydrothiazine **75**.



The foregoing syntheses are probably initiated by nucleophilic displacement reactions, in which the C—S bonds are first formed; the resultant intermediates then cyclize to species of type **59**, which spontaneously afford the products by the elimination of water. The method can be adapted for the preparation of 4-substituted 3,4-dihydro-2*H*-1,4-thiazines,^{45,55-57} and in special cases intermediates of type **59** are isolable. For example, the reaction



⁵⁵ Y. Avi-dor and J. Mager, *J. Biol. Chem.* **222**, 249 (1956).

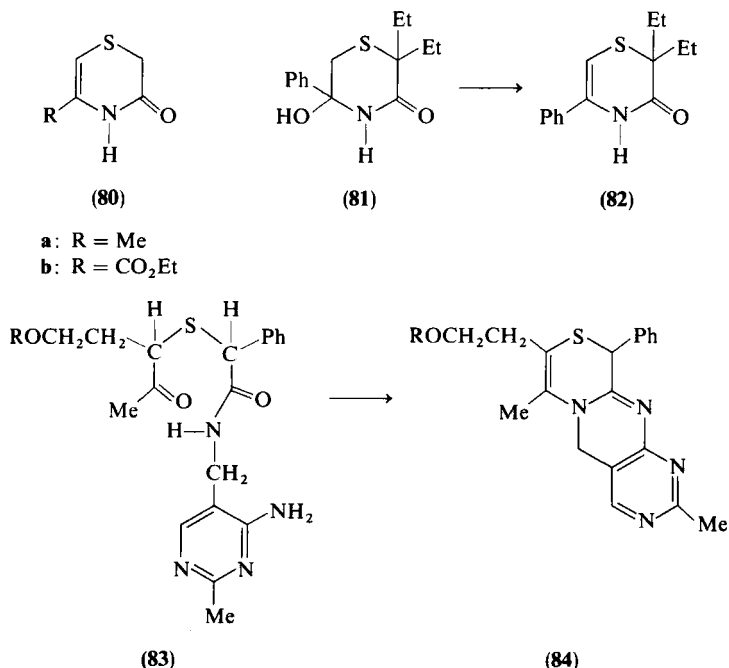
⁵⁶ D. B. Bryan, R. F. Hall, K. G. Holden, W. F. Huffman, and J. G. Gleason, *J. Am. Chem. Soc.* **99**, 2353 (1977).

⁵⁷ J. E. T. Corrie, J. R. Hlubucek, and G. Lowe, *J.C.S. Perkin I*, 1421 (1977).

of diphenylmethyl 3-bromo-2-oxopropionate with the mercaptoamide **77** afforded the compound **78**, which underwent dehydration to the dihydrothiazine **79** when treated with thionyl chloride.⁵⁶ Clearly, the bridgehead location of the nitrogen atom coupled with its amidic character are responsible for the lack of spontaneity of the dehydration.

d. *α-Mercaptoacetamides and α-Halo Aldehydes and Ketones*

The first example of this class, provided in 1948, involved the reaction of 2-mercaptoacetamide with 1-chloropropan-2-one.⁵⁸ Although the original investigators formulated the product as the thiazinol **13c**, subsequent workers showed that the tautomer **80a** was in fact produced.^{59,60} A variety of thiazinones of type **80** have now been prepared by the procedure, which constitutes a useful synthetic method. Furthermore, *N*-methyl 2-mercaptoacetamide can be used in place of 2-mercaptoacetamide.



2-Substituted 2-mercaptoacetamides have been successfully employed in the foregoing condensations.^{61,62} For example, the reaction of 2-ethyl-2-

⁵⁸ H. Sokol and J. J. Ritter, *J. Am. Chem. Soc.* **70**, 3517 (1948).

⁵⁹ G. De Stevens, A. Halamandaris, and L. Dorfman, *J. Am. Chem. Soc.* **80**, 5198 (1958).

⁶⁰ C. R. Johnson and C. B. Thanawalla, *J. Heterocycl. Chem.* **6**, 247 (1969).

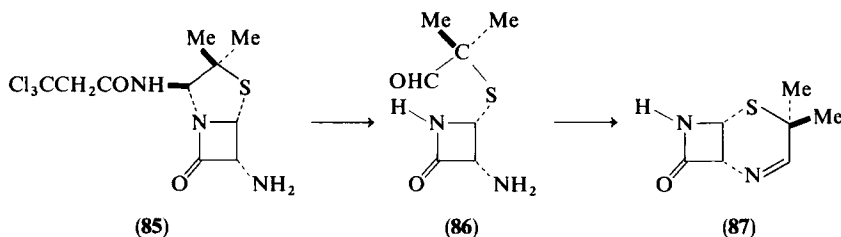
⁶¹ G. S. Skinner, J. S. Elmslie, and J. D. Gabbert, *J. Am. Chem. Soc.* **81**, 3756 (1959).

⁶² R. J. Stoodley, *Tetrahedron Lett.*, 941 (1967); *J. Chem. Soc. C*, 2891 (1968).

mercaptobutanamide with chloroacetophenone afforded a compound of probable structure **81**, which was converted into the thiazinone **82** when heated. Derivatives of type **83**, prepared from the appropriate mercaptoamide and chloroketone, underwent dehydrative cyclizations to give dihydrothiazines **84** when treated with phosphorus oxychloride.^{63,64}

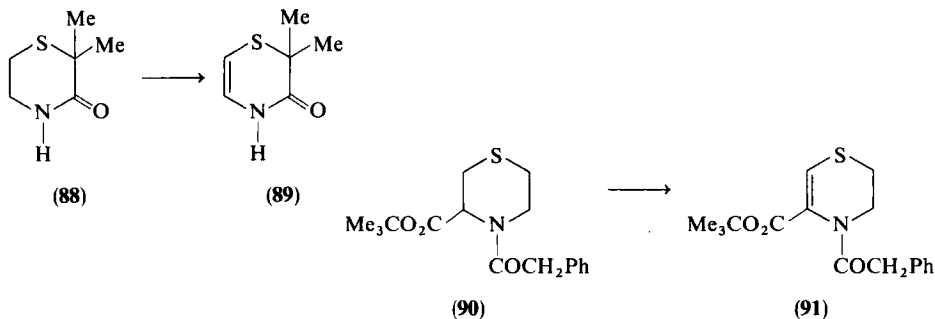
e. Penicillanic Acid Derivatives

The penicillin nucleus has been utilized for the construction of the dihydrothiazine ring.⁶⁵ Thus when treated with chromium(II) chloride, the penam **85** was converted into compound **87**; clearly, the amino aldehyde **86** is implicated in the reaction.



3. Oxidation of Tetrahydrothiazines

Tetrahydrothiazines may be converted into dihydrothiazines by oxidation with thionyl chloride⁶⁶ or chlorine.⁶⁷ For example, **88** afforded **89** when



⁶³ A. Takamizawa, Y. Hamashima, Y. Sato, H. Sato, S. Tanaka, H. Ito, and Y. Mori, *J. Org. Chem.* **31**, 2951 (1966).

⁶⁴ A. Takamizawa, Y. Hamashima, Y. Sato, and H. Sato, *Chem. Pharm. Bull.* **15**, 1178 (1967).

⁶⁵ G. Fechtig, H. Bickel, and K. Heusler, *Helv. Chim. Acta* **55**, 417 (1972).

⁶⁶ M. Nakanishi and T. Muro, *Yakugaku Zasshi* **91**, 166 (1971) [*CA* **74**, 125595 (1971)].

⁶⁷ D. M. Brunwin and G. Lowe, *J. Chem. Soc., Chem. Commun.*, 589 (1972); *J.C.S. Perkin I*, 1321 (1973).

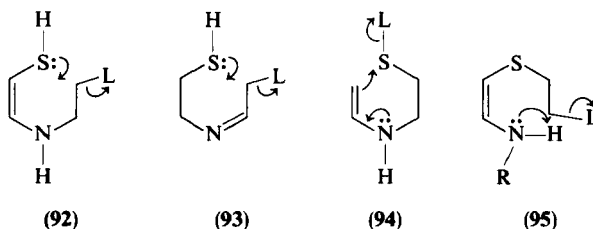
treated with the former oxidant. In principle, two isomeric dihydrothiazines may be formed by oxidation of compound **90**; however, chlorine at -70°C yielded only **91**.

4. Cyclization of Acyclic Precursors

Dihydrothiazines may be formed in a direct manner from appropriate acyclic species; the cyclization may involve either intramolecular nucleophilic displacement or intramolecular nucleophilic addition.

a. Intramolecular Nucleophilic Displacement

Four reactions of this type, depicted by the processes **92**–**95**, are implicated in the construction of dihydrothiazines. In all cases the precursors are reactive species that are generated only as intermediates.



An example of process **92** is provided by the reaction of thiazolium salts with dialkyl acylphosphonates; it provides a valuable synthetic entry to 5,6-dihydro-2*H*-1,4-thiazin-3-ones.

An insight into the mechanistic details of this transformation has been gained from the extensive studies of Takamizawa and co-workers.^{63,64,68–76} Initially, the reaction of thiamine hydrochloride (**96**) with diethyl benzoylphosphonate in the presence of sodium hydroxide was shown to give the dihydrothiazinone **97**. When the reaction was carried out in *N,N*-dimethylformamide containing triethylamine, compound **84** ($\text{R} = \text{H}$) was obtained;

⁶⁸ A. Takamizawa, Y. Sato, S. Tanaka, and H. Itoh, *Tetrahedron Lett.*, 3599 (1964); *Chem. Pharm. Bull.* **14**, 407, (1966).

⁶⁹ A. Takamizawa and Y. Sato, *Chem. Pharm. Bull.* **14**, 742 (1966).

⁷⁰ A. Takamizawa, T. Sato, and H. Sato, *Chem. Pharm. Bull.* **15**, 1183 (1967).

⁷¹ A. Takamizawa, Y. Hamashima, and H. Sato, *J. Org. Chem.* **33**, 4038 (1968).

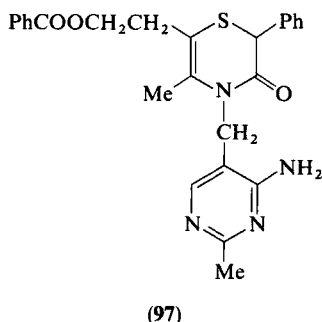
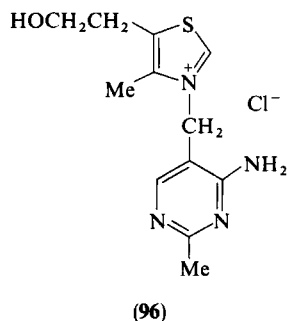
⁷² A. Takamizawa, Y. Mori, H. Sato, and S. Tanaka, *Chem. Pharm. Bull.* **16**, 1773 (1968).

⁷³ A. Takamizawa, Y. Hamashima, H. Sato, and S. Sakai, *Chem. Pharm. Bull.* **17**, 1356 (1969).

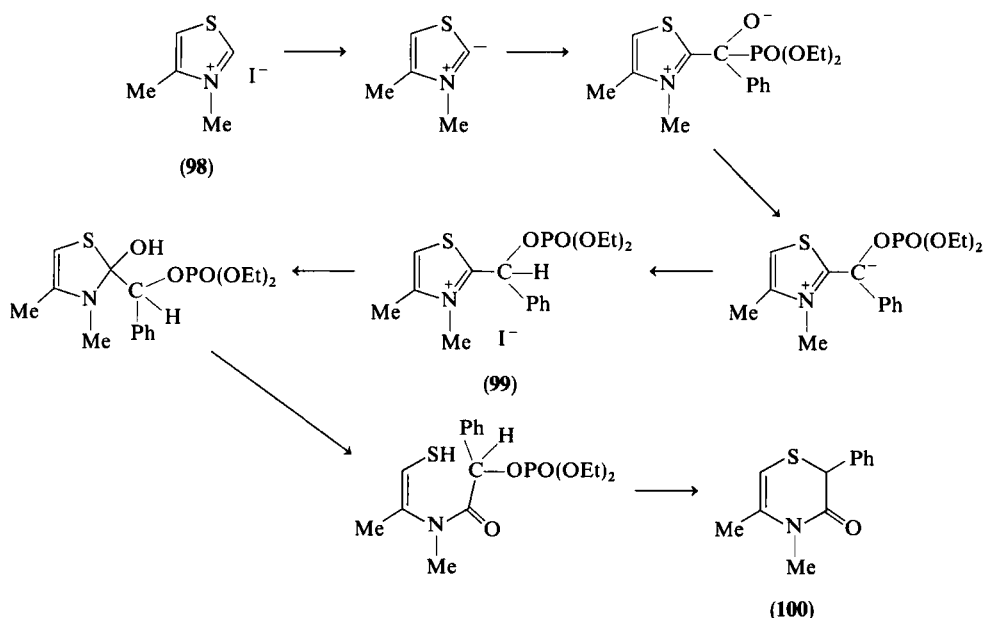
⁷⁴ A. Takamizawa, H. Sato, and Y. Sato, *Chem. Pharm. Bull.* **20**, 892 (1972).

⁷⁵ A. Takamizawa and H. Harada, *Chem. Pharm. Bull.* **21**, 770 (1973).

⁷⁶ A. Takamizawa and H. Harada, *Chem. Pharm. Bull.* **22**, 2818 (1974).



it was found to be a precursor of the derivative **97**. Further investigations indicated that simple thiazolium salts, e.g., **98**, also participated in the reaction; in these cases it was possible to isolate intermediates, e.g., **99**, which afforded the dihydrothiazinones, e.g., **100**, when treated with alkali. The pathway outlined in Scheme 4 provides a likely explanation for the course of the rearrangement.

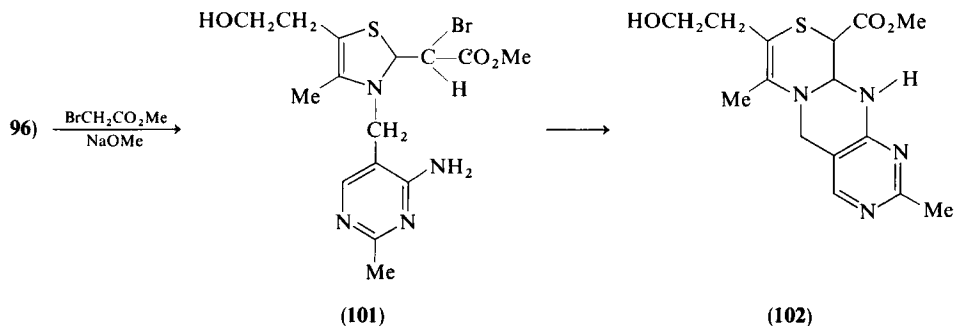


SCHEME 4

Thiazolium salts also react with α -bromocarbonyl compounds to give 5,6-dihydro-2*H*-1,4-thiazines.⁷⁷ Thus thiamine hydrochloride (**96**) afforded

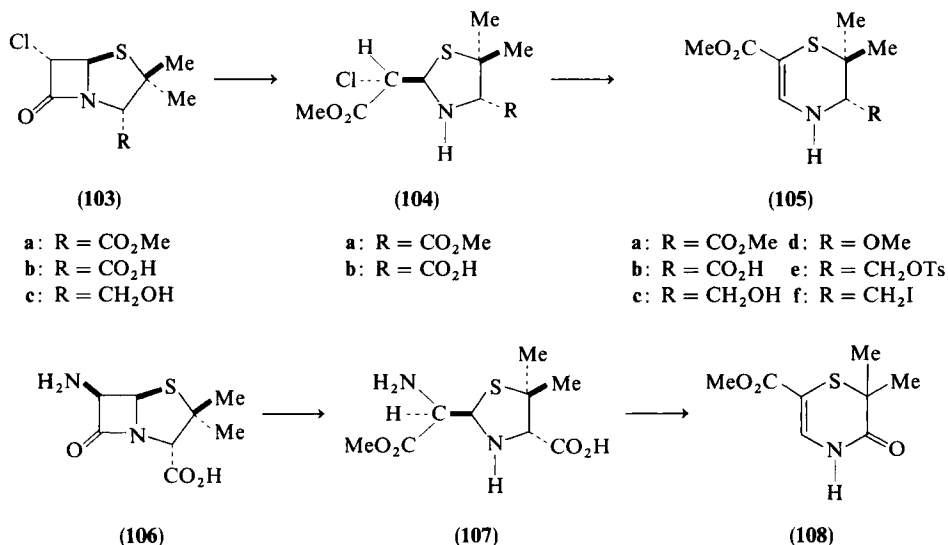
⁷⁷ S. Taeki and H. Hirano, *Takeda Kenkyusho Ho* **33**, 1 (1974) [*CA* **81**, 77863 (1974)].

the derivative **102** when treated with methyl bromoacetate and sodium methoxide; presumably the species **101** intervened.



Intermediates that undergo ring closures of type **93** are probably generated in the reactions of 6α -halopenicillanic acids with nucleophiles, and of β -mercaptoethylamines with either α -chloroaldehydes or 1,2-dibromoethenes.

The conversion of methyl 6α -chloropenicillanate (**103a**) into the dihydrothiazine **105a**, induced by methanolic sodium methoxide, has been shown to involve the intermediacy of the thiazolidine **104a**⁷⁸; the acid **103b** and the alcohol **103c** reacted in an analogous manner to give the compounds **105b** and **105c**.^{78,79} Corresponding reactions were observed using sodium azide



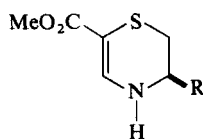
⁷⁸ I. McMillan and R. J. Stoodley, *Tetrahedron Lett.*, 1205 (1966); *J. Chem. Soc. C*, 2533 (1968).

⁷⁹ J. Kitchin and R. J. Stoodley, *J. Am. Chem. Soc.* **95**, 3439 (1973); *J.C.S. Perkin I*, 2460 (1973).

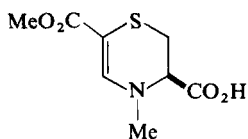
in *N,N*-dimethylformamide and, in the case of methyl 6 α -bromopenicillanate,⁸⁰ sodium ethoxide, benzylamine, dimethylamine, and phenylacetylhydrazine.

When treated with sodium nitrite in methanolic hydrogen chloride, 6 β -aminopenicillanic acid (**106**) was transformed into the dihydrothiazinone **108**.⁶² Although no intermediates were isolated, the derivatives **107** and **105b** were shown to afford the product **108** under the reaction conditions. The intermediacy of the thiazolidine **104b** was excluded, suggesting that the dihydrothiazine **105b** was probably formed by a deaminative ring expansion of **107**. The oxidative decarboxylation, involved in the conversion of the dihydrothiazine **105b** into product **108**, is discussed later (Section V,C,1,c).

The dihydrothiazine **105b** has also been prepared from D-penicillamine and methyl 2-chloro-3-oxopropionate.⁷⁸ In principle, its synthesis may involve a cyclization of type **93** or the dehydration of an intermediate of

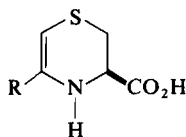


(109)

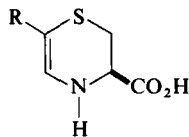


(110)

- a: R = H f: R = CHMe₂
 b: R = CO₂H g: R = CH₂I
 c: R = CH₂OH h: R = CD₂I
 d: R = CH₂OMs i: R = CONMe₂
 e: R = C(CH₂)Me j: R = Me



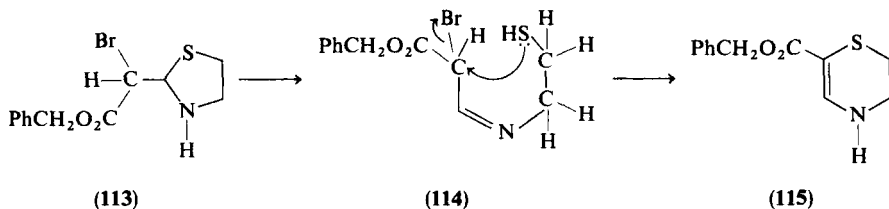
(111)



(112)

- a: R = CO₂Et
 b: R = CHO

- a: R = CO₂Et
 b: R = CHO



(113)

(114)

(115)

⁸⁰ N. Maggi and G. Gignarella, *Chem. Ind. (Milan)* **52**, 164 (1970).

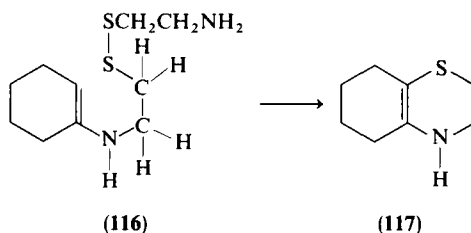
type **59**. The former pathway is preferred, however, since the thiazolidine **104b** and its diastereoisomers are the initial reaction products.⁸¹ β -Mercaptoethylamine, L-cysteine, and *N*-methyl L-cysteine reacted in an analogous manner with methyl 2-chloro-3-oxopropionate to give the dihydrothiazines **109a**, **109b**, and **110**.⁸² Interestingly, the reaction of L-cysteine with ethyl 2-chloro-3-oxopropionate and chloromalondialdehyde was first examined in 1944, during the Anglo-American penicillin program⁸³; at that time a distinction between the structures **111a** and **111b** or **112a** and **112b** for the products was not made.

β -Mercaptoethylamine reacts with α,β -dibromoacrylates and α,β -dibromomaleates to give dihydrothiazines.⁸⁴ The exclusive formation of **115**, in the case of benzyl α,β -dibromoacrylate, suggests that the cyclization **114** is involved; it seems likely therefore that the thiazolidine **113** intervenes.

Intermediates that undergo cyclizations of type **94** are probably generated in the reactions of thiazolidines with amines and sulfur, of bis(2-aminoethyl)disulfide with ketones under acidic conditions, and of 1,2-dithioles with sodium ethoxide.

When heated with elemental sulfur and *n*-butylamine, the thiazolidine **68** afforded a 3:1 mixture of the dihydrothiazines **66** and **67** in 38% yield; a likely reaction pathway is suggested in Scheme 5. Analogous reactions were observed with other 2,2-disubstituted thiazolidines.⁸⁵

The reaction of cyclohexanone with bis(2-aminoethyl)disulfide, under nitrogen and in the presence of toluene-*p*-sulfonic acid, afforded the dihydrothiazine **117** and 2-mercaptoethylamine, probably by way of the intermediate **116**; cyclooctanone, 2,6-dimethylheptan-4-one, and isopropyl phenyl ketone behaved similarly.⁸⁶



⁸¹ R. J. Stoodley, unpublished work (1967).

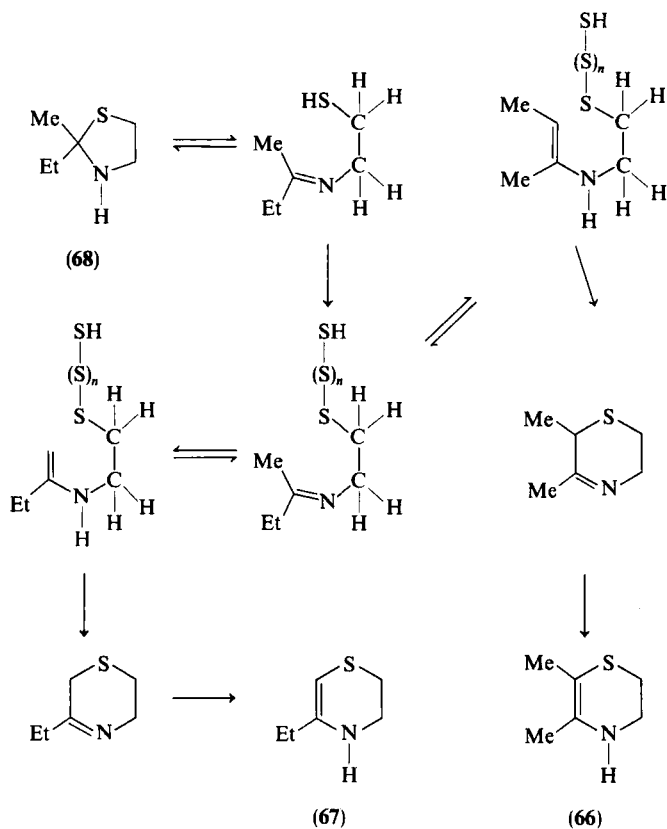
⁸² A. R. Dunn, I. McMillan, and R. J. Stoodley, *Tetrahedron* **24**, 2985 (1968).

⁸³ A. H. Cook and I. M. Heilbron, in "The Chemistry of Penicillin" (H. T. Clarke, J. R. Johnson, and R. Robinson, ed.), Ch. 25. Princeton Univ. Press, Princeton, New Jersey, 1949.

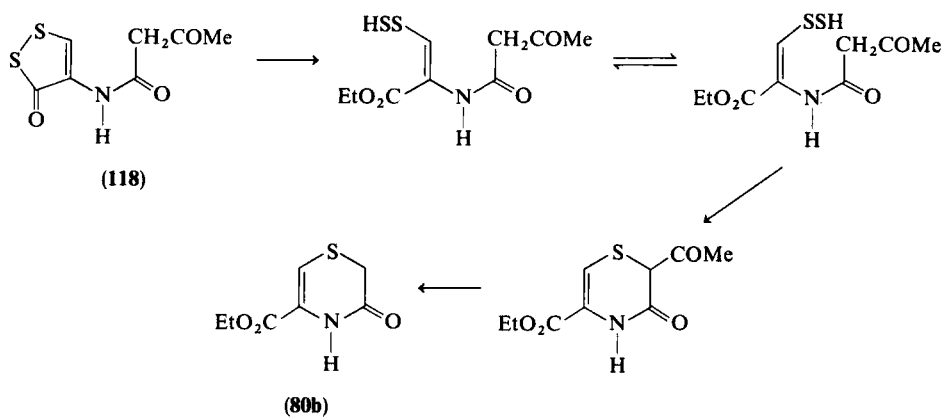
⁸⁴ J. Alexander, G. Lowe, N. K. McCullum, and G. K. Ruffles, *J.C.S. Perkin I*, 2092 (1974).

⁸⁵ F. Asinger, H. Offermanns, and D. Neuray, *Justus Leibigs Ann. Chem.* **739**, 32 (1970).

⁸⁶ F. M. Moracci, M. Cardellini, F. Liberatore, P. Marchini, G. Liso, and U. Gulini, *Int. J. Sulphur Chem. Part B* **8**, 341 (1973).



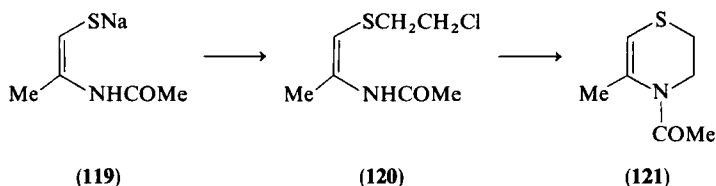
SCHEME 5



SCHEME 6

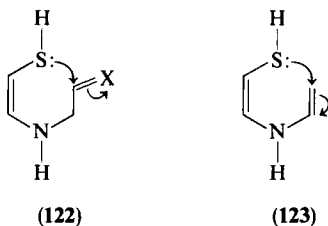
A low yield of the compound **80b** was isolated when the dithiole **118** was treated with sodium ethoxide⁸⁷; the product probably arose by the pathway outlined in Scheme 6.

An example of a ring closure of type **95** is provided by the conversion of compound **120** into the dihydrothiazinone **121** in the presence of sodium hydride.⁸⁸ The derivative **120** was prepared by treating the salt **119** with 1-bromo-2-chloroethane. The salt **119**, which is a versatile synthon (Section V,C,2,b), was generated as a stable species by the reduction of the dihydrothiazinone **80a** with sodium in liquid ammonia followed by the addition of one molar equivalent of ammonium chloride. Although the overall yield of the product **121** was low (24%) in the above case, the synthesis is of considerable potential.



b. Intramolecular Nucleophilic Addition

Two reactions of this type, depicted by processes **122** and **123**, are implicated in the construction of dihydrothiazines. In both cases, the precursors are generated only as intermediates.



An example of a cyclization of type **122** is provided by the conversion of the betaine **124**, prepared from 5-(2-hydroxyethyl)-3,4-dimethylthiazolium iodide and phenyl isothiocyanate, into the dihydrothiazine **125** in the presence of sodium hydroxide^{89,90}; a likely reaction pathway is suggested

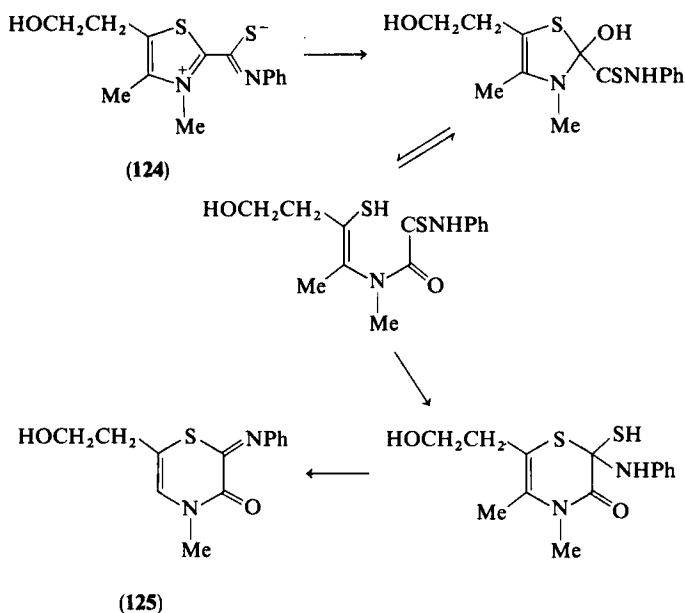
⁸⁷ R. F. C. Brown and I. D. Rac, *Aust. J. Chem.* **18**, 1071 (1965).

⁸⁸ S. Hoff, A. P. Blok, and E. Zwanenburg, *Tetrahedron Lett.*, 5199 (1972); *Rec. Trav. Chim. Pays-Bas* **92**, 879 (1973).

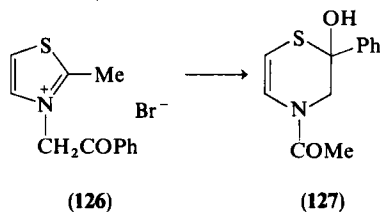
⁸⁹ A. Takamizawa, K. Hirai, and S. Matsumoto, *Tetrahedron Lett.*, 4027 (1968).

⁹⁰ A. Takamizawa, S. Matsumoto, and S. Sakai, *Chem. Pharm. Bull.* **22**, 293 (1974).

in Scheme 7. An analogous reaction ensues when the thiazolium salt is treated sequentially with a diarylcarbodiimide and sodium carbonate.^{89,91} The transformation of the thiazolium salt **126** into the dihydrothiazine **127** in the presence of sodium hydrogen carbonate further illustrates this mode of cyclization.⁹²



SCHEME 7

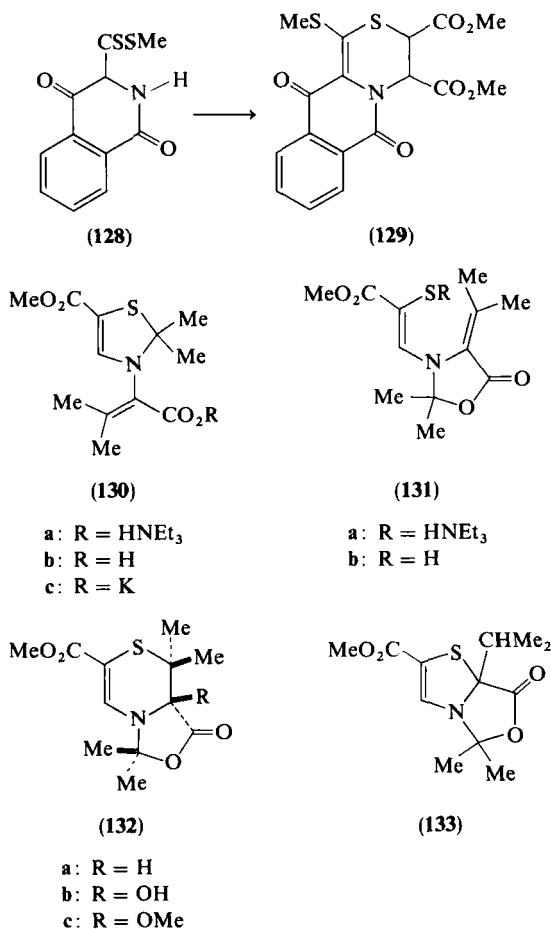


There is only one published example in which the dihydrothiazine ring is probably constructed by a cyclization reaction of type **123**; this involves the reaction of the compound **128** with dimethyl acetylenedicarboxylate

⁹¹ A. Takamizawa, S. Matsumoto, and I. Makino, *Chem. Pharm. Bull.* **22**, 311 (1974).

⁹² D. J. Adam and M. Wharmby, *Tetrahedron Lett.*, 3063 (1969).

to give the derivative **129**.⁹³ A further example, observed in the author's laboratory, is provided by the formation of the racemate of the compound **132a** from the salt **130a** in hot chloroform²⁴; it represents the reverse of a reaction which is discussed later (Section V,C,2,b). Interestingly, the acid **130b** reacts in a completely different manner to give the derivative **133**. This dichotomous behavior indicates that the thiolate **131a** undergoes the endocyclic conjugate addition whereas the thiol **131b** adds in an exocyclic anti-conjugate manner.



⁹³ S. Ueno, Y. Tominaga, R. Nasuki, Y. Matsuda, and G. Kobayashi, *Yakugaku Zasshi* **94**, 607 (1974) [*CA* **81**, 120391 (1974)].

C. REACTIVITY

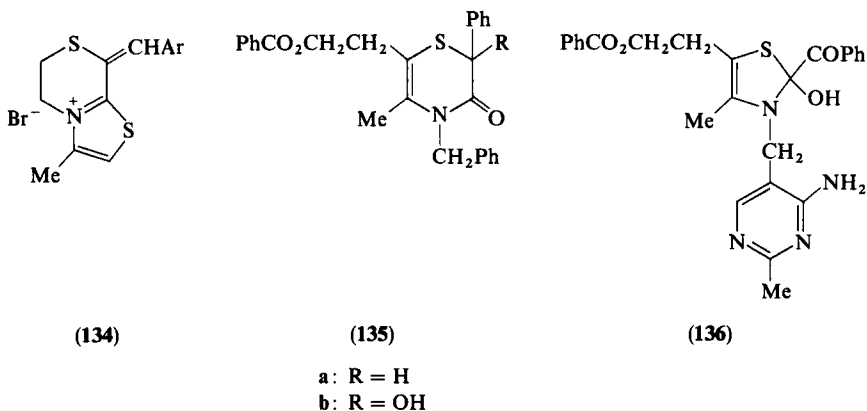
1. Retention of the Dihydrothiazine Ring

a. Position 1

There are numerous examples in which dihydrothiazines are converted into their 1-oxides and 1,1-dioxides; these reactions are discussed in Sections VI,B,1 and VII,B,1, respectively.

b. Position 2

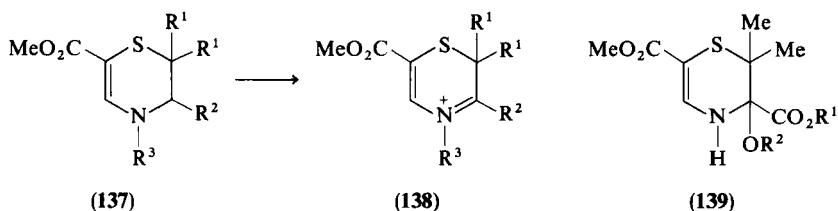
The hydrogen atoms at position 2 of dihydrothiazines of types **51** and **80** are expected to display acidic properties; this behavior has been reported only in the case of the thiazolium salt **54**, which afforded the arylidene derivative **134** with an aromatic aldehyde.⁴⁰ When treated with hydrogen peroxide in acetic acid, the dihydrothiazinone **135a** was converted into the 2-hydroxy derivative **135b**⁷⁴; by contrast, compound **97** afforded the thiazoline **136** (Section V,C,2,b). Clearly the position of the equilibrium between the two possible products is dramatically influenced by the nature of the *N*-substituent.



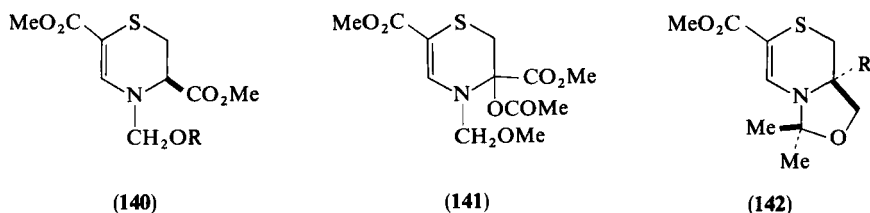
c. Position 3

A large number of reactions involving position 3 of 3,4-dihydro-2*H*-1,4-thiazines have been described. It is appropriate to divide these into two categories: those in which the 3-substituents are replaced, and those in which they are modified.

Dihydrothiazines of type **137** readily undergo oxidation at position 3; although the products isolated depend upon the oxidant, the reaction conditions, and the substituents, it seems likely that thiazinium ions **138** intervene. Thus, when left in acetone containing toluene-*p*-sulfonic acid monohydrate, compounds **105a** and **132a** underwent autoxidation to give the racemates of derivatives **139a** and **132b**^{81,94}; they were also transformed into the racemates of the methoxy derivatives **139b** and **132c** with either mercury(II) acetate in methanol or sodium nitrite in methanolic hydrogen chloride.^{23,62} The last-described reagents, however, differed in their reactivity toward the acid **105b**; the racemate of the methoxy derivative **105d** was formed using mercury(II) acetate in methanol, and the dihydrothiazinone **108** was produced with sodium nitrite in methanolic hydrogen chloride. Control experiments suggested that the compound **108** was formed by way of the derivative **139c** and that the dihydrothiazine **105d** was not an intermediate in the reaction.⁶²



- a: $R^1 = Me$; $R^2 = H$
 b: $R^1 = R^2 = Me$
 c: $R^1 = R^2 = H$



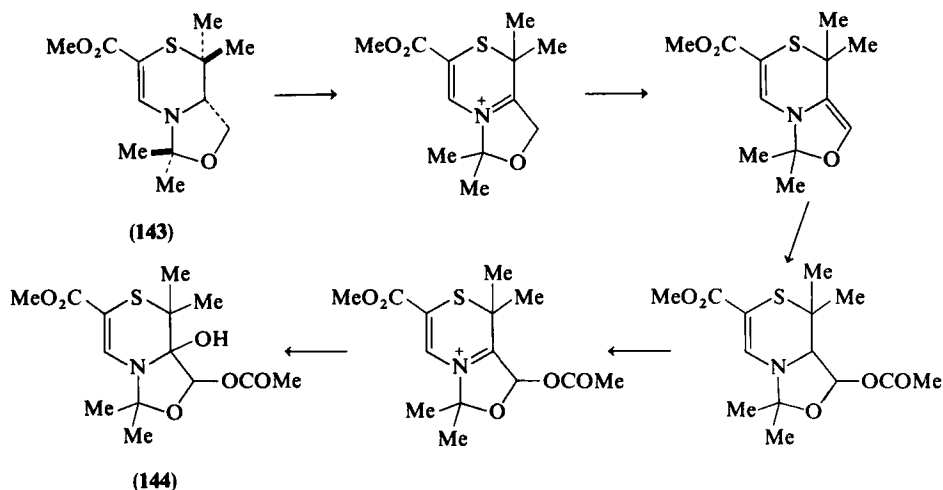
- a: $R = Me$
 b: $R = H$
 c: $R = COMe$

- a: $R = H$
 b: $R = OCOMe$
 c: $R = OH$
 d: $R = OEt$

Lead tetraacetate in benzene has also been used to effect the oxidation of dihydrothiazines of type **137**.²³ For example, the reagent converted compounds **18a** and **140a** into the derivatives **19** and **141**. The presence of an

⁹⁴ I. McMillan and R. J. Stoodley, unpublished work (1967).

activating group at position 3 of the dihydrothiazine ring is not essential for the success of this oxidation, since **142a** was transformed into the racemate of the acetate **142b**. Interestingly, compound **143** afforded the derivative **144**, when treated with the oxidant; a likely reaction pathway is suggested in Scheme 8.



SCHEME 8

In addition to their involvement in oxidation reactions, thiazinium ions of type **138** intervene in the interconversion of 3-hydroxy and 3-alkoxy dihydrothiazines.^{62,95} For example, compound **139b** was converted into **139a** by aqueous hydrochloric acid.

The oxo moiety of dihydrothiazinones, e.g., **80a**, has been replaced with the thio group by using phosphorus pentasulfide.^{40,60} Derivatives of type **84** readily underwent hydrolysis to give thiazinones, e.g., **97**; the reverse reaction was achieved by using phosphorus oxychloride.^{63,64,72}

The majority of reactions in which substituents at position 3 have undergone modification have used the dihydrothiazines **105b** and **109b** as starting materials. Although reduction of **18a** was achieved with sodium borohydride in methanol, the derived alcohol **109c** was largely racemic; epimerization at position 3 was avoided, however, by the use of lithium borohydride in dioxane.⁹⁶ Diborane effected the reduction of the ester **105a** to the alcohol **105c**, but lithium borohydride was the preferred reagent.⁹⁷ The foregoing

⁹⁵ R. J. Stoodley and R. B. Wilkins, *J.C.S. Perkin I*, 1572 (1974).

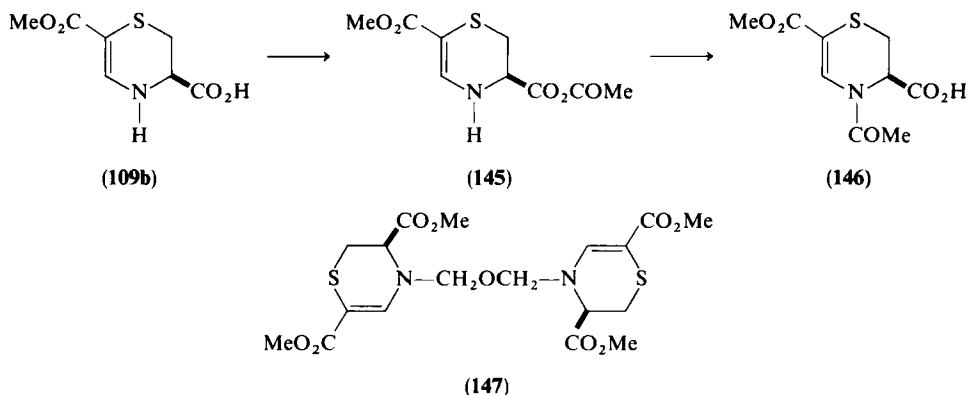
⁹⁶ A. R. Dunn and R. J. Stoodley, *Tetrahedron Lett.*, 2979 (1969); *Tetrahedron* **28**, 3315 (1972).

⁹⁷ A. R. Dunn and R. J. Stoodley, *Chem. Commun.*, 1368 (1969); *J. Chem. Soc.*, 2509 (1972).

results reveal that the methoxycarbonyl group at position 3 is more susceptible to nucleophilic attack than is that at position 6, in accord with the vinylogous urethan character of the latter group. The greater reactivity of the O—H group compared with the N—H moiety of the derivatives **109c** and **105c** is emphasized by the exclusive formation of esters, e.g., **109d** and **105e**, in the presence of acid chlorides.^{96,97} When treated with hydrogen and palladium, **109e** underwent reduction to give **109f**; there was no evidence for hydrogenation of the C=C bond of the dihydrothiazine ring.⁹⁷

d. Position 4

By virtue of their enamine or imine nature, the nitrogen atoms of dihydrothiazines of types **50** and **51** are expected to display weakly basic and weakly nucleophilic properties. Both types of compound are reported to form salts with picric acid⁴⁴; derivatives of type **50** also react with phenyl isocyanate to give phenylcarbamates and undergo acetylation with acetic anhydride, formylation with formic acid,^{44,46} and methylation with methyl iodide.⁴⁵ Dihydrothiazines of types **105** and **109** are expected to be less reactive, because their nitrogen atoms possess vinylogous urethan character. Thus, attempts to acetylate the derivative **18a** with acetyl chloride were unsuccessful. By contrast, the acid **109b** was readily converted into the acetyl derivative **146**; undoubtedly, the reaction involved an acyl transfer from the intermediate anhydride **145**.⁹⁸ Although it is not possible to effect its *N*-methylation (Section V,C,1,c), the compound **18a** reacted readily with formaldehyde in the presence of dilute hydrochloric acid to give the carbinolamine **140b**; the dimer **147** was formed when the last compound was left in acidic dioxane.



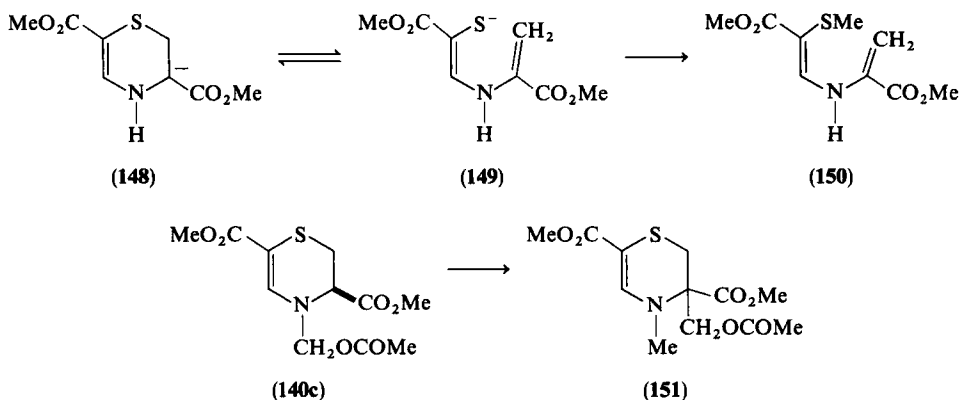
⁹⁸ A. G. W. Baxter and R. J. Stoodley, *J.C.S. Perkin I*, 2540 (1976).

The dimer **147** and the carbinolamine **140b** reacted with alcohols in the presence of an acidic catalyst to give the corresponding alkoxymethyl derivatives, e.g., **140a**.⁹⁸ Nitrosation of the N—H group, to give the *N*-nitroso compound **18b**, readily occurred when the dihydrothiazine **18a** was treated with sodium nitrite and hydrochloric acid in aqueous dioxane.⁸¹

There is only one report of the *N*-alkylation of a dihydrothiazinone; this involves the *N*-methylation of the derivative **80a** in the presence of methyl iodide and sodium hydride.⁵⁹

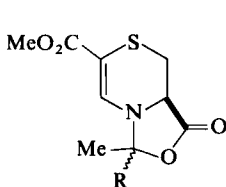
e. Position 3 and 4

The hydrogen atom of position 3 of the derivative **18a** is expected to display acidic properties. Thus when treated with sodium methoxide in methanol- d_1 , the ester **18a** underwent racemization with incorporation of deuterium at position 3.⁹⁴ In principle, the carbanion **148**, the species formally involved in the foregoing reaction, may isomerize to the enethiolate **149** by a β -elimination process. There is good evidence (Section V,C,2,b) that such isomerizations do occur and are reversible (Section V,B,4,b). Normally, alkylating agents selectively trap species of type **149**; thus compound **150** was isolated when the derivative **18a** was treated with sodium hydride and methyl iodide.⁹⁹ However, in the presence of potassium *t*-butoxide and methyl iodide, the derivative **140c** was converted into **151**; evidence for the intermolecular nature of the reaction was provided by the observation that the same product was formed when a 1:1 mixture of the derivatives **18c** and **140c** was treated with the base.²⁴



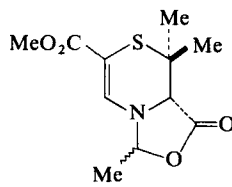
⁹⁹ A. G. W. Baxter and R. J. Stoodley, *J. Chem. Soc., Chem. Commun.*, 251 (1975); *J.C.S. Perkin I*, 584 (1976).

In the presence of 2,2-dimethoxypropane and an acidic catalyst,^{82,100} the acids **105b** and **109b** were converted into the derivatives **132a** and **152a**. Corresponding reactions occurred with acetaldehyde to give **153**, as a single diastereoisomer, and **152b**, as a 1.5:1 mixture of diastereoisomers; the configurations of the products were not established.⁹⁹ Oxazolidinones of the foregoing type have been of interest as precursors of thiazolines (Section V,C,2,b). They also react with sodium hydroxide to regenerate their acid precursors and with lithium borohydride to give the alcohols **105c** and **109c**.⁹⁵ In the hope of preparing the alcohol **105c**, selectively monodeuteriated at the 3-methylene group, the behavior of the compound **154** toward lithium borodeuteride, lithium aluminum deuteride, lithium tri-*t*-butoxy-aluminum deuteride, and sodium borodeuteride was examined; however, the reductions occurred only with a low selectivity.¹⁰⁰ The oxazolidinol **154** was prepared from compound **132a** by reduction with sodium aluminum hydride.¹⁰⁰ Diborane converted **152a** into the *N*-isopropyl alcohol **155a**.¹⁰¹

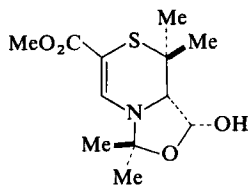


(152)

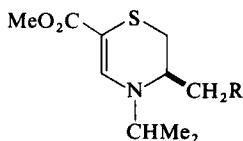
a: R = Me
b: R = H



(153)



(154)



(155)

a: R = OH
b: R = I

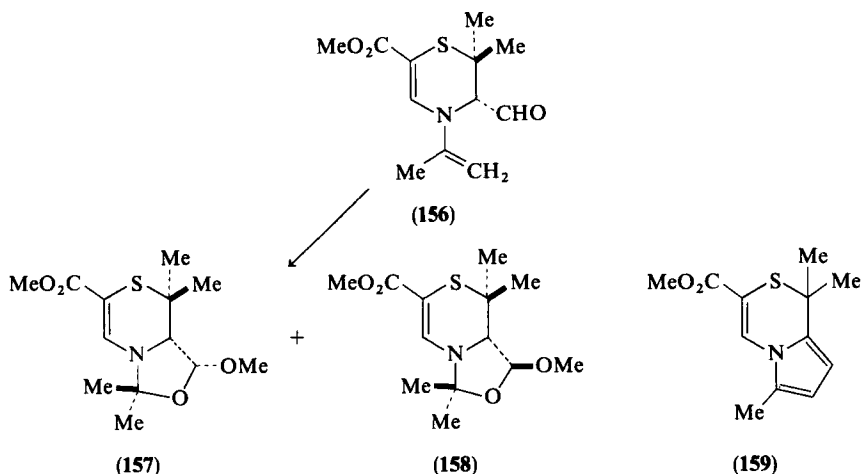
The hydroxy group of the oxazolidinol **154** was rapidly replaced by the methoxy group in the presence of methanolic hydrogen chloride.¹⁰² Whereas

¹⁰⁰ J. Kitchin and R. J. Stoodley, *J. Chem. Soc., Chem. Commun.*, 959 (1972); *J.C.S. Perkin I*, 22 (1973).

¹⁰¹ J. Kitchin and R. J. Stoodley, *Tetrahedron* **29**, 3023 (1973).

¹⁰² J. Kitchin and R. J. Stoodley, *J.C.S. Perkin I*, 1985 (1973).

a 1.5:1 mixture of the diastereoisomers **157** and **158** was formed after 10 seconds, the derivative **158** was the sole product after 40 minutes. When the reaction was conducted in the presence of methanol- d_1 , deuterium was incorporated into the methyl groups attached to the oxazolidine ring, providing evidence for the intervention of the species **156**. The hydroxy group of the compound **154** was also replaced by the methylthio group in the presence of methanethiol containing an acidic catalyst; however, the configuration of the product, which was obtained as a single isomer, was not established.¹⁰² The species **156** is also implicated in the conversion of **154** into **159**, a reaction that is induced by methanesulfonyl chloride, toluene-*p*-sulfonyl chloride, or aluminum chloride.¹⁰²

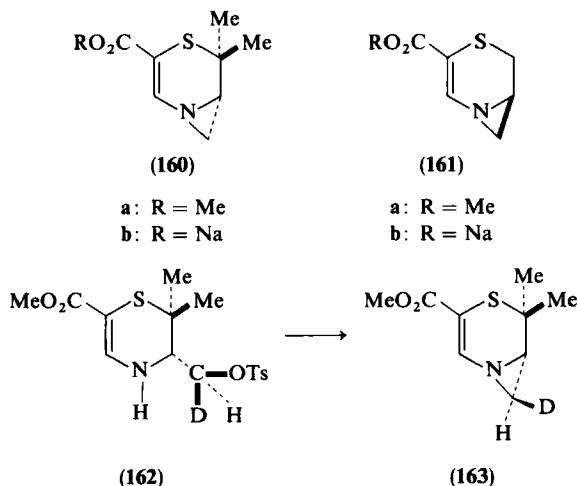


The alcohols **105c** and **109c** reacted with acetone in the presence of an acidic catalyst to give the oxazolidines **143** and **142a**; the products were reconverted into the reactants under aqueous acidic conditions.^{96,102}

When treated with sodium hydride in tetrahydrofuran, the compounds **105e** and **109d** were transformed into the bicyclic aziridines **160a** and **161a**.^{96,97} It is generally assumed that such ring closures proceed with an inversion of configuration at the methylene group, and this assumption has been substantiated in the case of the derivative **162**; the monodeuteriated tosylate **162** was converted exclusively into the monodeuteriated aziridine **163**.⁷⁹ As may be expected, the bicyclic aziridines **160a** and **161a** readily react with cleavage of the aziridine rings, particularly under acidic conditions. Although, in principle, two modes of cleavage are feasible, reagents always rupture the N—CH₂ bond.^{96,97,103} This regioselectivity is probably con-

¹⁰³ A. R. Dunn and R. J. Stoodley, *Tetrahedron Lett.*, 3367 (1969).

trolled by electronic factors rather than steric ones. Thus, in the transition state leading to cleavage of the N—CH₂ bond, the electron pair developing on the nitrogen atom is able conjugatively to interact with the π -electrons of the α,β -unsaturated ester moiety.



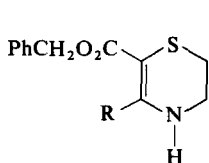
f. Position 5

Only two reactions involving the replacement of substituents at position 5 of 3,4-dihydro-2H-1,4-thiazines have been described. Thus, in the presence of sodium ethoxide, the chlorine atom of the derivative **56** was replaced by an ethoxy group,⁴¹ and, when heated at 140°–150°C, compound **164a** underwent decarboxylation to give **164b**.⁸⁴ There are a number of examples in which modification of the 5-substituent occurs.^{45,56,57,67,84} For example, when treated with lithium aluminum hydride, the acid **164a** was reduced to the aldehyde **164c**.⁸⁴

g. Position 6

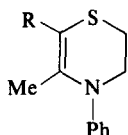
As already mentioned (Section V.C,1,c), the alkoxycarbonyl groups of 3,4-dihydro-2H-1,4-thiazine-6-carboxylates are relatively unreactive to nucleophilic attack because of their vinylogous urethan character. However, when treated with sodium hydroxide followed by acid, the derivative **165a** was converted into **165b**⁴⁵; evidently, the competing conjugative interaction of the nitrogen lone-pair electrons with the phenyl group is responsible for this behavior. The spontaneity of the decarboxylation is also of interest; possibly this is due to the presence of the β -keto acid **166** in low concentration.

The derivatives **160a** and **161a** also underwent saponification under mild conditions¹⁰³; in these examples, the vinylogous urethan character of the methoxycarbonyl group is dampened by the constraining effects of the three-membered ring.



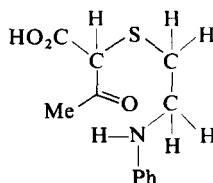
(164)

a: R = CO₂H
b: R = H
c: R = CHO

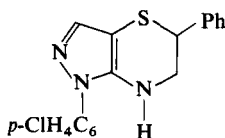


(165)

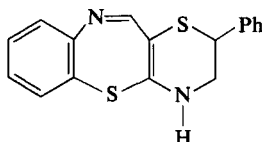
a: R = CO₂Et
b: R = H



(166)



(167)



(168)

h. Positions 5 and 6

Two reactions involving the construction of a new ring at position 5 and 6 of the dihydrothiazine **56** have been described. Thus, when treated with *p*-chlorophenylhydrazine⁴¹ and 2-mercaptoaniline,¹⁰⁴ compound **56** was converted into the products **167** and **168**.

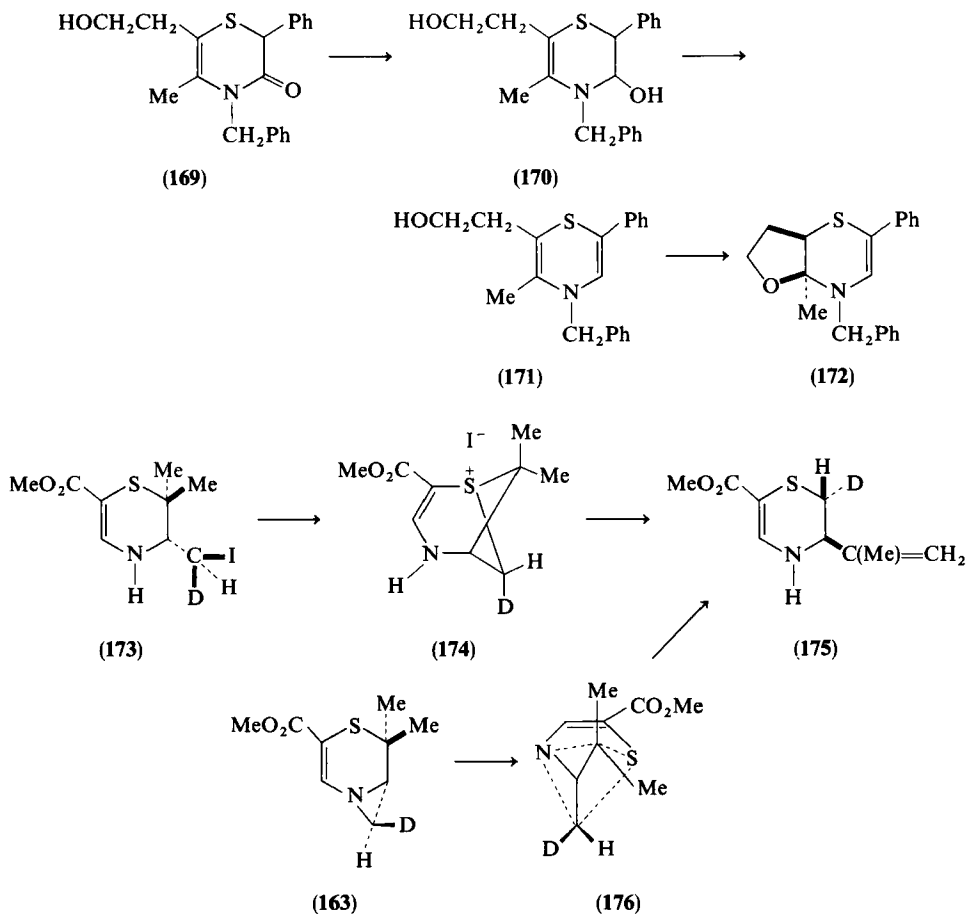
i. Rearrangements

A number of rearrangements are known in which new dihydrothiazines are formed from existing derivatives. One example, in which the ring skeleton remains unaltered, is provided by the conversion of compound **169** into **172** in the presence of lithium aluminum hydride⁶⁹; presumably the intermediate dihydrothiazinol **170** undergoes dehydration to the thiazine **171**, which cyclizes to the product.

When heated in butan-2-one for 10 days, the iodide **109g** underwent racemization; NMR and mass spectroscopy revealed that the racemization

¹⁰⁴ O. Aki, Y. Nakagawa, and K. Shirakawa, *Takeda Kenkyusho Ho* **31**, 159 (1972) [*CA* **77**, 152135 (1972)].

of the dideuteriated iodide **109h** was accompanied by a scrambling of the isotope between the ring and the exocyclic methylene groups.¹⁰⁵ Consequently, a 1,3-sulfur migration was involved. Further studies showed that the aziridine **161a** was not an intermediate and that the racemization was remarkably insensitive to solvent effects.⁹⁷ Racemization also occurred when the 4-position of the dihydrothiazine ring was substituted, as in the case of the derivative **155b**.¹⁰⁶



The iodide **105f** was converted into the compound **109e** when heated in butan-2-one for 5 days; again, the aziridine **160a** was shown not to be an

¹⁰⁵ A. R. Dunn and R. J. Stoodley, *Chem. Commun.*, 1169 (1969).

¹⁰⁶ J. Kitchin and R. J. Stoodley, unpublished work (1972).

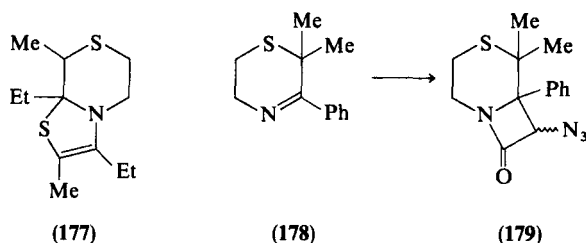
intermediate.⁹⁷ The stereochemistry of the 1,3-sulfur migration was investigated by using the specifically monodeuteriated iodide **173**, and the isotope was located at the 2 α -position of the product, i.e., **175**.⁷⁹ This result indicated that the methylene group underwent an inversion of configuration during the sulfur shift and implicated the intervention of the ion pair **174**.

Although not an intermediate in the foregoing reaction, the aziridine **160a** was transformed into **109e** when heated in boiling toluene for 4 days.⁹⁷ Labeling experiments employing the specifically monodeuteriated aziridine **163** revealed that the 1,3-sulfur migration occurred with retention of configuration to give only the derivative **175**⁷⁹; the structure **176** represents a possible transition state for this interesting reaction.

2. Loss of the Dihydrothiazine Ring

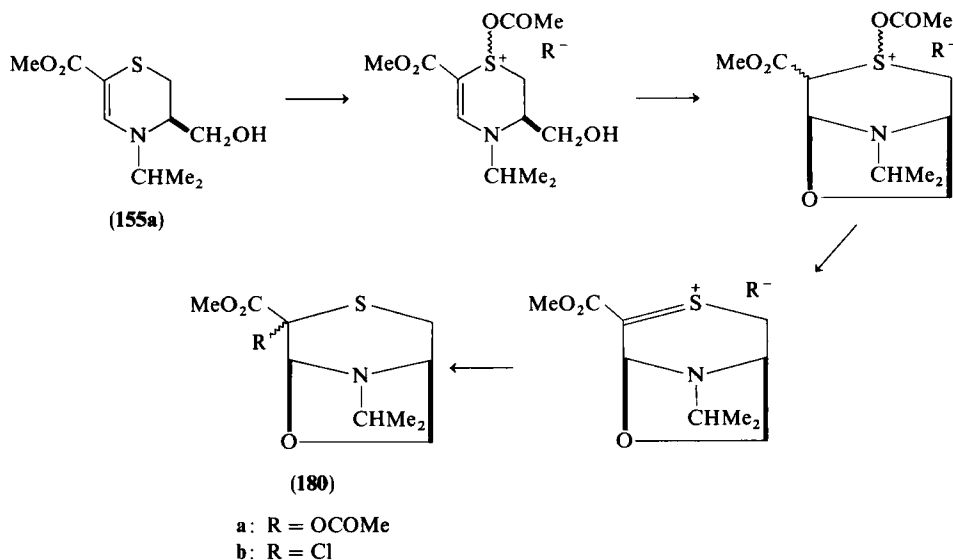
a. No Change of the Ring Skeleton

The oxidative conversion of dihydrothiazines to thiazines has already been mentioned (Section II,B).



In principle, additions may occur to the C=C or C=N bonds of dihydrothiazines. There are many examples of such reactions. Thus α -mercapto-ketones readily react with both 3,4- and 5,6-dihydro-2*H*-1,4-thiazines^{44,46}; the formation of the derivative **177** from the reaction of 2-mercaptopentan-3-one and the compound **60a** provides an illustration. A possible [2 + 2]cycloaddition involving azidoketene is implicated in the formation of the adduct **179**, as a single diastereoisomer, from the reaction of the dihydrothiazine **178** with azidoacetyl chloride and triethylamine.⁴⁷ A variety of reagents, including formic acid,^{44,46,49,51} sodium borohydride,^{46,51,86} lithium aluminum hydride,⁵¹ and hydrogen sulfide,⁴⁶ has been employed to effect the reduction of dihydrothiazines to tetrahydrothiazines. There is one example involving an oxidative addition to the C=C bond of the derivative **155a**; thus, in the presence of lead tetraacetate and acetic acid, the bicyclic com-

pound **180a** was formed.¹⁰⁷ This reaction probably proceeds by the route suggested in Scheme 9; related cyclizations are discussed later (Section V,I,C,2).



SCHEME 9

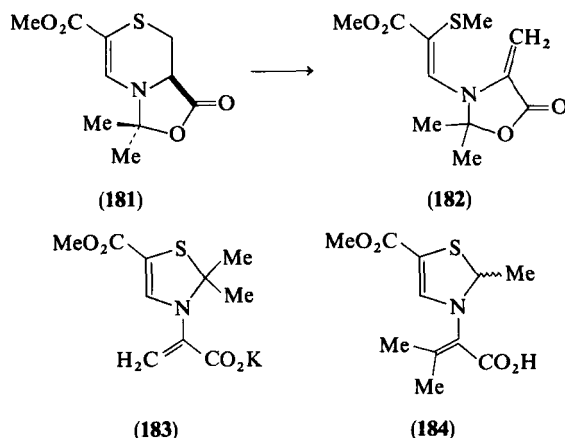
b. Change of the Ring Skeleton

There are many reactions that result in the conversion of dihydrothiazines into other heterocycles. They may be divided into three categories: those that involve a nonoxidative and nonreductive cleavage, those that require an oxidative cleavage, and those that proceed by a reductive cleavage of the dihydrothiazine ring.

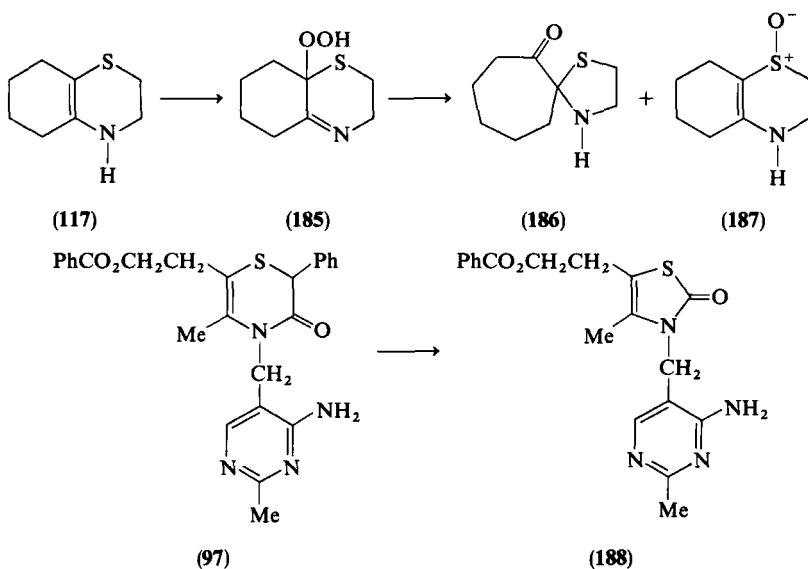
As already mentioned (Section V,C,l,e), the 1—2 bonds of 5,6-dihydro-2*H*-1,4-thiazines bearing an acidic hydrogen atom at position 3 can be cleaved under basic conditions by β -elimination reactions; thus the dihydrothiazine **181** was converted into **182** when treated with potassium *t*-butoxide in the presence of methyl iodide.⁹⁹ In the absence of the alkylating agent, the thiazolines **183** and **130c** were formed from the compounds **181** and **132a**. In the hope of unraveling the stereochemistry of these reorganizations, the behavior of the derivative **153**, as a single diastereoisomer of unestablished configuration, was examined; it was converted into the thiazoline **184** of

¹⁰⁷ J. Kitchin and R. J. Stoodley, *J.C.S. Perkin I*, 2464 (1973).

high optical activity. This result suggested that the displacement occurred with inversion of configuration.

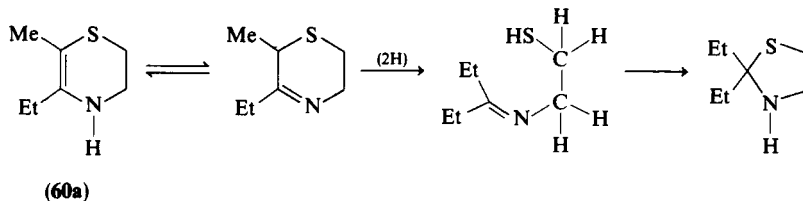


A number of oxidative ring contractions of dihydrothiazines are known. For example, when a cyclohexane solution of the compound **117** was exposed to the air at room temperature, a 1:1 mixture of the derivatives **186** and **187** was produced, probably by way of the hydroperoxide **185**.⁸⁶ As already indicated (Section V.C,1,a), the product of the reaction of the dihydrothiazinone **97** with hydrogen peroxide and acetic acid was the thiazoline **136**⁶⁸; other examples of this oxidative ring contraction have been de-

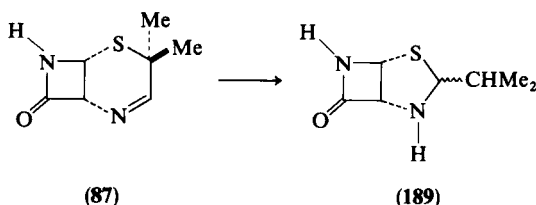


scribed.^{72,108} When chromium trioxide was employed as the oxidant, the corresponding thiazolinones, e.g., **188**, were isolated.⁶⁸

With hydrogen sulfide in the presence of a base, dihydrothiazines undergo reductive ring contraction to give thiazolidines, usually in good yield^{48,85,109}; for example, 2,2-diethylthiazolidine was formed from the compound **60a**. ³⁵S-Labeling experiments are consistent with the pathway outlined in Scheme 10.¹⁰⁹ Zinc in acetic acid is also a useful reagent for effecting such reactions⁶⁵; thus it promoted the conversion of the dihydrothiazine **87** into **189**.



SCHEME 10



Mention has already been made of the reductive cleavage of the thiazinone **80a** to the salt **119** (Section V,B,4,a); the species **119** has proved to be a versatile synthon for the preparation of heterocycles^{88,110,111} (cf. Scheme 11).

c. Rupture of the Ring Skeleton

A number of reactions of dihydrothiazines which afford ring-opened products have been described. Such reactions may occur under nonoxidative conditions, in the presence of oxidizing agents, or in the presence of reducing agents.

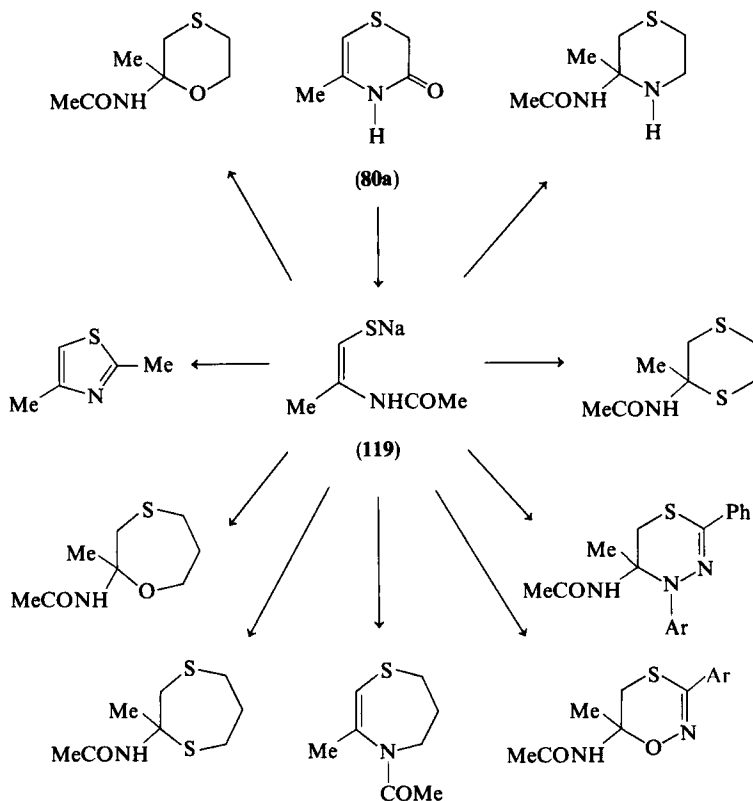
In principle, dihydrothiazines may undergo hydrolytic ring openings. Such processes occur under acidic or basic conditions when the product is an amide.^{42,58,68} Normally, however, the ring-opened compounds are unstable with respect to their precursors; in such instances, the addition of a hydrazine

¹⁰⁸ A. Takamizawa, Y. Sato, and S. Tanaka, *Chem. Pharm. Bull.* **14**, 588 (1966).

¹⁰⁹ F. Asinger, A. Saus, and D. Neuray, *Justus Liebigs Ann. Chem.* **759**, 121 (1972).

¹¹⁰ S. Hoff, A. P. Blok, and E. Zwanenburg, *Rec. Trav. Chim. Pays-Bas* **92**, 890 (1973).

¹¹¹ S. Hoff and E. Zwanenburg, *Rec. Trav. Chim. Pays-Bas* **92**, 929 (1973).

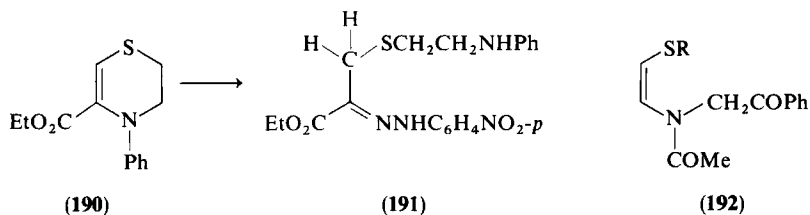


SCHEME 11

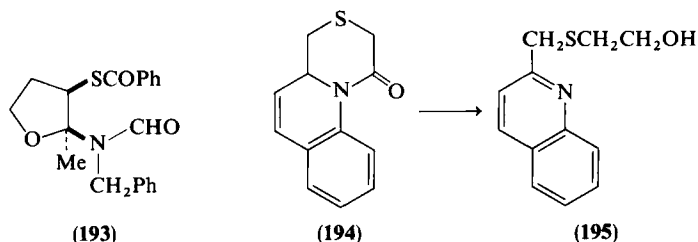
derivative may promote the reaction.⁴⁵ For example, the hydrazone **191** was formed when the derivative **190** was left in the presence of *p*-nitrophenylhydrazine under acidic conditions. The dihydrothiazinol **127** was converted into the acetate **192b** when treated with acetic anhydride, in accord with its equilibration with the ring-opened tautomer **192a**.⁹²

The only example of an oxidative ring opening of the dihydrothiazine ring involves the ozonolysis of the derivative **172** to give compound **193**.⁶⁹

The 1—2 bond of dihydrothiazinones can be reductively cleaved in the presence of sodium in liquid ammonia.⁸⁸ Thus compound **80a** was converted into the salt **119** (Section V,B,4,a); although a stable isolable material, **119** readily underwent *S*-alkylation when treated with alkyl halides.^{88,110,111} Although Raney nickel is expected to effect the reductive desulfurization of dihydrothiazines, only one example of this reaction has been reported; thus the compound **80b** afforded *N*-acetylalanine ethyl ester.⁸⁷ The 3—4 bond of dihydrothiazinones can be reductively cleaved under certain circum-



a: $\text{R} = \text{H}$
b: $\text{R} = \text{COMe}$



stances. For example, derivative **194** is converted into the quinoline **195** by sodium borohydride¹¹²; evidently, the aromatic stabilization gained by the product provides the driving force for the reaction.

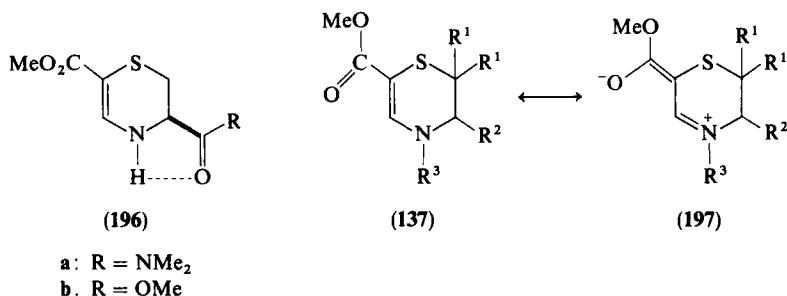
D. PHYSICOCHEMICAL PROPERTIES

1. Infrared Spectra

The N—H stretching frequencies have been reported for a wide variety of 4-unsubstituted 3,4-dihydro-2*H*-1,4-thiazines; the absorptions, which are of medium intensity, appear in the $3360\text{--}3380\text{ cm}^{-1}$ region.^{44,49,78,82,84,86,96,97} IR Spectroscopy has been used to study the association of such compounds.⁸² Thus, in dilute chloroform solution (0.01 M), the dihydrothiazine **109a** shows an absorption at 3486 cm^{-1} attributable to nonassociated N—H; in more concentrated solution (0.5 M), it displays a broad peak at 3365 cm^{-1} due to intermolecularly hydrogen bonded N—H. Compound **109i** absorbs at 3393 cm^{-1} in dilute chloroform solution, for the intramolecularly hydrogen-bonded species **196a**. Compound **18a** possesses two peaks, ca. 1:2.5, at 3428 and 3462 cm^{-1} ; the former band is due to nonassociated species, and the latter to the intramolecularly bonded species **196b**. The N—H stretching

¹¹² P. Neelakantan, N. Rao, U. T. Bhalarao, and G. Thyagarajan, *Indian J. Chem.* **11**, 1051 (1973) [*CA* **80**, 8272 (1974)].

frequencies of 4-unsubstituted 3,4-dihydro-2*H*-1,4-thiazin-3-ones generally appear in the 3100–3250 cm^{-1} region.^{59,61,62,87}



3,4-Dihydro-2*H*-1,4-thiazines display absorptions due to C=C stretching vibrations; the frequency of the absorption is influenced by the type of substituents attached to the double bond. Thus, when the substituents are alkyl groups and/or hydrogen atoms, a strong band is observed in the 1640–1660 cm^{-1} region.^{44,49,86} In derivatives of type 137, the absorption, which is also strong, is shifted to lower frequency (1590–1615 cm^{-1}).^{78,82,84,96,97}

In accord with the conjugative interaction 197, the methoxycarbonyl group of derivatives of type 137 displays a C=O stretching frequency at ca. 1660 cm^{-1} when R³ is a hydrogen atom^{78,82,84,96,97} and at ca. 1685 cm^{-1} when R³ is an alkyl group.^{82,96,100–102} The C=O moiety of 3,4-dihydro-2*H*-1,4-thiazin-3-ones usually absorbs in the 1640–1690 cm^{-1} region.^{59,61,62,73,74,76,87}

5,6-Dihydro-2*H*-1,4-thiazines display C=N absorptions, which generally appear in the 1640–1655 cm^{-1} region.^{46,49,65,86}

2. Ultraviolet Spectra

Surprisingly, the UV spectra of alkyl derivatives of 3,4-dihydro-2*H*-1,4-thiazine (50) have not been reported. However, the $\ddot{\text{S}}-\text{C}=\text{C}-\ddot{\text{N}}$ chromophore of alkyl derivatives of 3,4-dihydro-2*H*-1,4-thiazin-3-one appears as a medium-intensity band (ϵ 2300–2450) in the 293–308 nm region.^{59,69} The introduction of an alkoxycarbonyl group shifts the absorption to longer wavelength and increases its intensity, but the effect is apparently independent of the position of substitution; thus compounds 80b and 108 show absorption maxima at 320 nm (ϵ 5800)⁸⁷ and 322 nm (ϵ 5700),⁶² respectively.

The UV spectra of a large number of methyl 3,4-dihydro-2*H*-1,4-thiazine-6-carboxylates, e.g., 105 and 109, have been determined. In general, such compounds show three absorption maxima at ca. 215, 260, and 310 nm; the short-wavelength absorption is usually of medium intensity (ϵ ca. 7000),

that at 260 nm is usually less intense (ϵ ca. 3000), and the 310 nm absorption is usually the strongest band (ϵ ca. 10,000).^{78,82,96,97} The long-wavelength absorptions are clearly the result of $n \rightarrow \pi^*$ transitions involving the $\ddot{\text{N}}-\text{C}=\text{C}(\text{CO}_2\text{Me})-\ddot{\text{S}}$ chromophore.

5,6-Dihydro-2H-1,4-thiazines should absorb weakly owing to the $n \rightarrow \pi^*$ transitions of the $\text{C}=\ddot{\text{N}}$ group. The only reported UV spectrum is that of **87**, which absorbs at 269 nm (ϵ 105).⁶⁵

3. Nuclear Magnetic Resonance Spectra

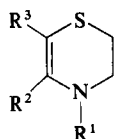
The protons at position 2 of dihydrothiazines of type **198** appear in the δ 2.80–3.00 region^{82,84}; as expected, these protons experience a downfield shift (to ca. δ 3.36) in the case of the thiazinone **80b**.⁸⁷ The NMR spectra of several dihydrothiazines of type **199** have been reported, and the 2-protons absorb in the δ 2.30–3.50 region.^{82,96,97,101} In principle, compounds of type **199** may exist as a rapidly interconverting mixture of the conformers **200** and **201**; usually there is a preference for one of these conformers (Section V,D,4). Since axial protons generally absorb at higher field strength than their equatorial counterparts, the chemical-shift differences between H_a and H_b can be used to probe the conformational equilibrium; in general, a negative value of ($\delta \text{H}_a - \text{H}_b$) suggests a preference for the conformer **201** whereas a positive value is indicative of the conformer **200**.^{82,96}

The protons at position 3 of dihydrothiazines of type **198** appear at significantly lower field than those at position 2; they absorb in the δ 3.55–3.80 region.^{82,84}

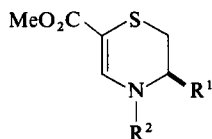
An analysis of several derivatives of types **199a,b** and **202a,b** reveal that the 5-proton appears in that δ 7.45–7.75 region.^{78,82,84,96–102} As expected, the introduction of an acyl group at position 4 of such compounds causes a significant deshielding of the 5-proton; thus that of **18a** absorbs at δ 7.61⁸² and that of the *N*-acetyl derivative **18d** at δ 8.14.⁹⁸

The 6-proton of derivatives of type **203a,b** resonates in the δ 5.38–5.63 region^{73,74,76}; by contrast, that of **80b** appears at δ 6.73 in accord with the mesomeric influence of the ethoxycarbonyl group.⁸⁷

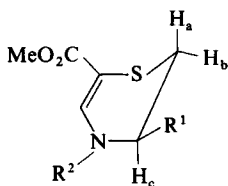
The 2-methylene group of dihydrothiazines of type **199** shows a geminal coupling constant of 12.5–13.2 Hz^{82,96,97,101} whereas the 3-methylene group of compound **127** possesses a coupling constant of 14 Hz.⁹² The vicinal coupling constants of the 2- and 3-protons of derivatives of type **199** have been used to probe the conformational behavior of such molecules. In general, the conformer **200** is characterized by $J_{ac} = 9.8$ Hz and $J_{bc} = 3.3$ Hz and the conformer **201** by $J_{ac} = J_{bc} = 3.3$ Hz.^{82,96} In the case of derivatives of type **199a**, the 4-hydrogen atom usually couples weakly with the 3-proton



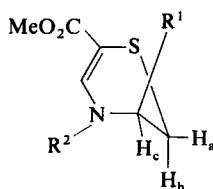
(198)

a: $R^1 = H$ 

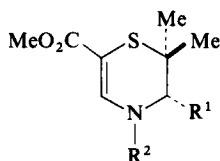
(199)

a: $R^2 = H$ b: $R^2 = \text{alkyl}$ 

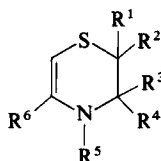
(200)

a: $R^2 = H$ 

(201)

a: $R^2 = H$ 

(202)

a: $R^2 = H$ b: $R^2 = \text{alkyl}$ 

(203)

a: $R^6 = H$ b: $R^6 = \text{alkyl}$

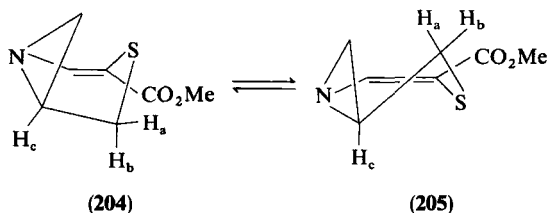
($J = 3 \text{ Hz}$)⁷⁸ and more strongly with the 5-proton ($J = 6-7 \text{ Hz}$).^{78,82,96,97} The 5- and 6-protons of compound **127** are reported to show a coupling constant of 8 Hz.⁹² Long-range coupling ($J = 1.0-1.6 \text{ Hz}$) occurs between the 2- and 6-protons of dihydrothiazinones, e.g., **100**.^{73,74,76}

There is very little information on the NMR spectral properties of 5,6-dihydro-2H-1,4-thiazines. The vinylic proton of **87** absorbs at δ 8.04 and it displays long-range coupling ($J = 2.3 \text{ Hz}$) with the 4-proton.⁶⁵

4. Conformational Behavior

On the assumption that atoms 1, 3, 4, 5, and 6 of 3-substituted methyl 3,4-dihydro-2H-1,4-thiazine-6-carboxylates are approximately coplanar [because of the conjugative interaction between the nitrogen moiety and the methoxycarbonyl group (Section V,D,1)], derivatives of type **199** are

expected to exist as a rapidly interconverting mixture of the conformers **200** and **201**. The conformational equilibrium has been probed by NMR spectroscopy.^{82,96,97,101} Compounds of type **199**, e.g., **18c,d**, **140a-c**, and **155a,b**, exist predominantly as the conformer **201**; evidently, the severe allylic interaction between R^1 and R^2 in the conformer **200** is avoided. The conformational behavior of compounds of type **199a** depends upon the nature of R^1 . When the 3-substituent is a nonpolar group, as in the case of the derivatives **109e,f,j**, it appears that there is an equal preference for the conformers **200** and **201**. However, when the 3-substituent is a polar group, as with the compounds **109c,d,g**, the conformer **201a** is markedly favored; this effect has been ascribed to a nonbonded stabilizing interaction between the sulfur atom and the substituent at position 3. In contrast with the foregoing examples, the dihydrothiazine **109i** exists predominantly as the conformer **200a**; IR spectroscopic studies (Section V,D,1) have shown that this behavior is the result of a strong intramolecular hydrogen bond between the N—H and the C=O moiety of the amido group. The conformational behavior of compound **18a** is of special interest because of its solvent dependence. In a nonpolar solvent, the opportunity for intramolecular hydrogen bonding results in a preference for the conformer **200a**; however, in a polar medium, the intermolecular hydrogen bonding is destroyed by the solvent and the conformer **201a** is favored.

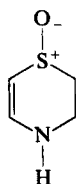


In principle, the bicyclic aziridine **161a** may be represented by the conformers **204** and **205**. NMR spectroscopic studies have revealed that **205** is preferred; a similar result is observed with compounds **161b** and **160a,b**.¹⁰³

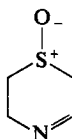
VI. Dihydro-1,4-thiazine 1-Oxides

A. TAUTOMETRIC BEHAVIOR

Two tautomeric structures, **206** and **207**, are possible for dihydro-1,4-thiazine 1-oxide; only derivatives of the former compound have been described.



(206)



(207)

B. SYNTHESIS

Dihydrothiazine oxides have been much less studied than dihydrothiazines. The available syntheses may be divided into two types, which reflect the nature of the immediate precursor of the dihydrothiazine oxide ring.

1. Oxidation of Dihydrothiazines

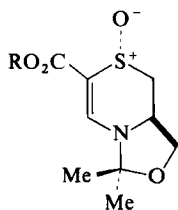
The most widely used method for the preparation of dihydrothiazine oxides involves the oxidation of the parent dihydrothiazines with sodium periodate or *m*-chloroperbenzoic acid.^{79,95,98,100-102,113,114} In certain instances, oxygen will act as the oxidant; for example, the sulfoxide **187** was formed when a cyclohexane solution of the compound **117** was exposed to the air.^{44,46,86} The mechanism of this reaction, in which the thiazolidine **186** was a co-product, has already been discussed (Section V,C,2,b).

The oxidation of chiral dihydrothiazines may, in principle, lead to two sulfoxides. In general, there is a marked preference for the formation of one of these diastereoisomers; thus the derivatives **142a**, **152a**, and **161a** yielded exclusively the (*R*)-oxides **208a**, **209**, and **210**. A total or a high preference for the formation of the (*R*)-oxides, e.g., **211a**, was also observed during the oxidation of dihydrothiazines of type **199a**. However, with derivatives of the type **199b**, mixtures of sulfoxides were produced; thus **155a** afforded a 2.3:1 mixture of the (*S*)-oxide **212** and the (*R*)-oxide **213**.

The foregoing results indicate that, in the case of the conformationally constrained systems **142a**, **152a**, and **161a**, there is a marked preference for the oxidant to donate an oxygen atom to the sulfur moiety from the axial direction. Presumably, in the transition state leading to the equatorial sulfoxide, a significant allylic interaction between the oxidant and the

¹¹³ A. G. W. Baxter, J. Kitchin, R. J. Stoodley, and R. B. Wilkins, *J. Chem. Soc., Chem. Comm.*, 285 (1973).

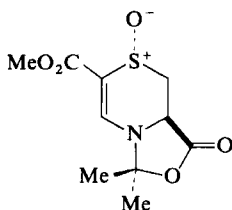
¹¹⁴ R. J. Stoodley and R. B. Wilkins, *J. Chem. Soc., Chem. Commun.*, 796 (1974); *J.C.S. Perkin I*, 716 (1975).



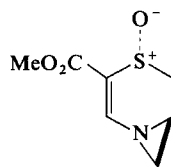
(208)

a: R = Me

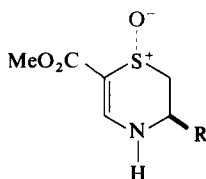
b: R = Na



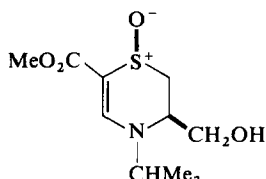
(209)



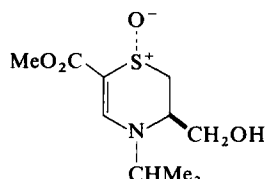
(210)



(211)



(212)



(213)

a: R = CO₂Meb: R = CH₂OCOMec: R = CH₂OHd: R = CO₂H

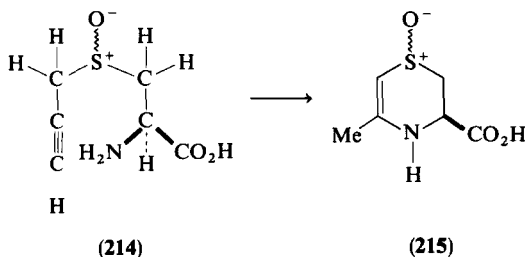
methoxycarbonyl group is required; equatorial attack is therefore avoided. In principle, derivatives of type **199** may exist as the conformers **200** and **201**, both of which may undergo oxidation. Assuming that only axial attack is permissible, the conformer **200** will lead to the (*R*)-oxide, and the conformer **201** to the (*S*)-oxide. Axial attack of the former conformer requires the involvement of an allylic interaction between R¹ and R²; axial attack of the latter conformer necessitates the development of a 1,3-interaction between the oxidant and R¹. The outcome of the oxidation is therefore expected to depend upon the magnitude of these two interactions. As the size of R² increases, the allylic interaction will get larger and a greater percentage of the oxidation will proceed by way of the conformer **201**; more of the (*S*)-oxide is therefore expected as the size of R² increases.

2. Cyclization of Acyclic Precursors

The only example in which a dihydrothiazine oxide is formed in a direct manner from an acyclic precursor involves the ammonia-induced cyclization of the acetylene **214** to the sulfoxide **215**.¹¹⁵ Although both isomers of the

¹¹⁵ J. F. Carson and L. E. Boggs, *J. Org. Chem.* **36**, 611 (1971).

reactant were available, only one underwent the cyclization; its configuration and that of the product were not established.

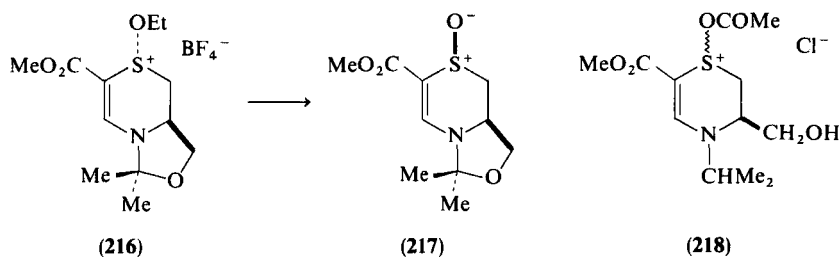


C. REACTIVITY

1. Retention of the Dihydrothiazine Oxide Ring

a. Position 1

The conversion of dihydrothiazine oxides into dihydrothiazine dioxides is discussed later (Section VII,B,1). Treatment of the sulfoxide **208a** with triethyloxonium tetrafluoroborate yielded the salt **216**, which was converted into the (*S*)-oxide **217** by sodium hydroxide.¹⁰¹ The formation of the same sulfoxonium salt **218**, of unestablished configuration at sulfur, was observed by NMR spectroscopy when the sulfoxides **212** and **213** were treated with acetyl chloride in [²H₃]methyl cyanide at -35°C .¹⁰⁷



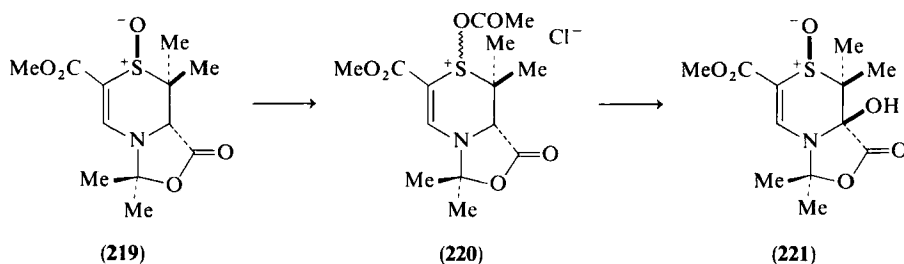
b. Position 2

The hydrogen atoms at position 2 of 2-unsubstituted dihydrothiazine oxides are expected to possess acidic properties. Thus, when treated with sodium deuterioxide in deuterium oxide, the compound **208b** underwent deuterium exchange of the hydrogen atoms adjacent to the sulfinyl group;

no selectivity was observed.¹¹⁶ Deuterium exchange of the corresponding hydrogen atoms of compound **208a** was achieved by using potassium *t*-butoxide and [²H₆]dimethyl sulfoxide; in this instance, the α -hydrogen atom exchanged ca. 3.5 times faster than the β -hydrogen atom.¹¹⁶

c. Position 3

Autoxidation of compound **219** has been reported to occur in the presence of two molar equivalents of acetyl chloride and oxygen; the product **221** was isolated in racemic form.¹¹⁴ Since no reaction occurred in the absence of acetyl chloride, the acetoxonium salt **220** is implicated as the species that undergoes the autoxidation.



A number of trivial reactions involving the modification of the 3-substituent have been described^{95,101,102}; for example, when treated with methanolic sodium methoxide, the acetate **211b** was converted into the alcohol **211c**.

d. Positions 3 and 4

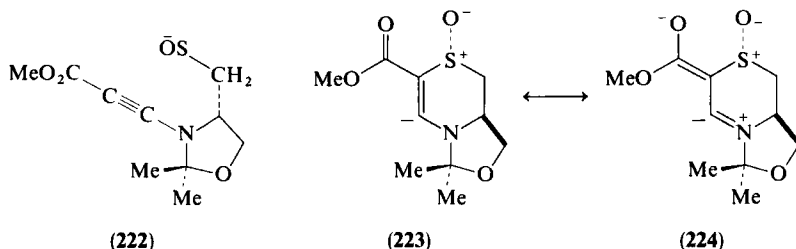
The oxazolidinone hydrogen atom of the compounds **209** and **219** displays acidic properties (Section VI,C,1). Although it is possible to effect the hydrolysis of the former substance with sodium hydroxide, to give the acid **211d** in optically pure form, the latter substance undergoes partial racemization prior to hydrolysis.⁹⁵ Under acidic conditions, compound **208a** is converted into the alcohol **211c**; however, more forcing conditions are required to effect the reaction than that involving substance **152a**.¹⁰¹

e. Position 5

Somewhat surprisingly, the vinylic hydrogen atom of derivative **208a** shows appreciable acidity; it underwent deuterium exchange, at room temperature

¹¹⁶ A. J. Anderson, J. Kitchin, and R. J. Stoodley, *Tetrahedron Lett.*, 3379 (1973).

in the presence of potassium *t*-butoxide and [$^2\text{H}_6$]dimethyl sulfoxide, slightly faster than the α -hydrogen atom on the carbon moiety adjacent to the sulfinyl group.¹¹⁶ The vinylic hydrogen atom of compound **217** behaved in a similar manner. Since the stereochemical integrity of the sulfinyl group was maintained during the foregoing reactions, the involvement of species **222** is negated. Evidently, the vinyl anion, e.g., **223**, intervenes and its formation is facilitated by the resonance contribution **224**.



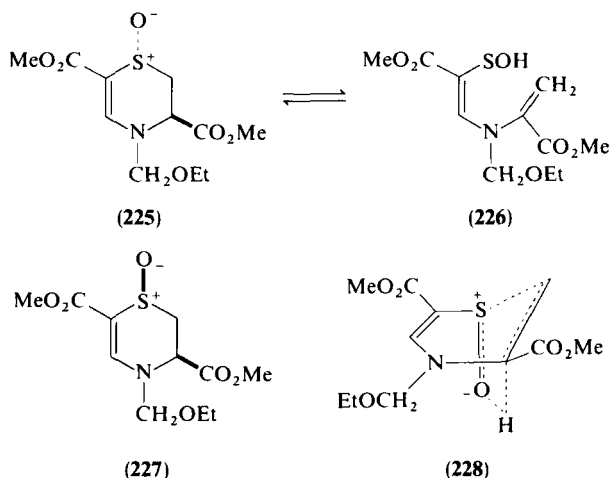
f. Position 6

In contrast with compound **152a**, the sulfoxide **208a** is readily converted into the salt **208b** by sodium hydroxide.¹¹⁶ The basis for this increased reactivity of the methoxycarbonyl group is not understood, particularly as the carbonyl moiety of both groups appears in the IR region at 1680 cm^{-1} .

g. Rearrangements

Dihydrothiazine oxides, possessing a carbonyl moiety at position 3 oriented anti with respect to the sulfinyl oxygen atom, readily racemize under mild conditions.^{95,98,113} For example, compound **225** was converted into its enantiomer when left in chloroform solution at room temperature. When conducted in the presence of methanol- d_1 , the racemization was accompanied by deuterium incorporation at the 3-position, implicating the intermediacy of the sulfenic acid **226**. In accord with the requirements for a syn-axial arrangement of the migrating hydrogen atom and the sulfinyl group, compound **227** was recovered unchanged when heated in boiling toluene for 4 days. The foregoing results suggest that the racemization is a pericyclic reaction in which the 1,4-hydrogen shift occurs by way of the transition state **228**.

Previously, it was noted that dihydrothiazines possessing an acidic hydrogen atom at position 3 underwent β -elimination reactions (Section V,2,b). Corresponding processes are implicated in the interconversion of the sulfoxides **225** and **227** in the presence of 1,5-diazabicyclo[4.3.0]non-5-ene; a 1:4.5 mixture of the derivatives **225** and **227** was present at equilibrium.⁹⁵



2. Loss of the Dihydrothiazine Oxide Ring

a. No Change of the Ring Skeleton

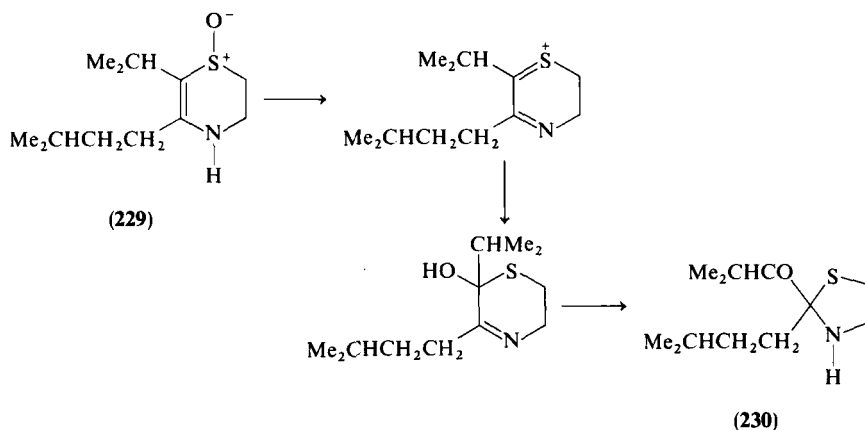
An unusual Pummerer-like reaction has been reported to occur when certain 3-hydroxymethyl dihydrothiazine oxides are treated with acetyl chloride.^{100,107} For example, the compounds **212** and **213** were converted into the bicyclic derivative **180b**, which was isolated as a 4:1 mixture of diastereoisomers. The reaction probably occurs by a pathway similar to that depicted in Scheme 9.

In contrast with the sulfoxide **208a** which was converted into its diastereoisomer **217**, compound **209** was transformed into a mixture of the racemates of the derivatives **142c** and **142d** when treated with triethyloxonium tetrafluoroborate followed by sodium hydroxide.⁹⁵ A similar rearrangement occurred with the sulfoxide **219** under corresponding conditions and in the presence of acetyl chloride under nitrogen; the formation of the racemate of the compound **132b** in the latter instance is to be contrasted with the formation of the racemate of **221** in the presence of acetyl chloride under oxygen (Section VI,C1,c).¹¹⁴

b. Change of the Ring Skeleton

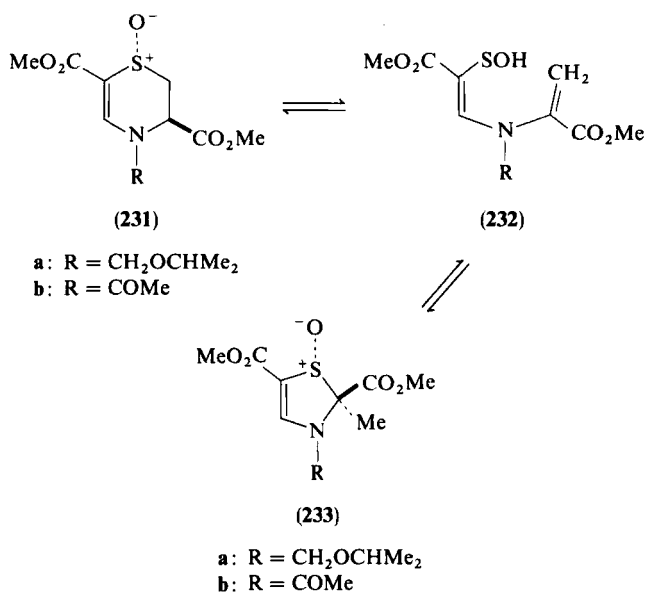
There are two examples in which dihydrothiazine oxides are converted into other heterocycles; ring contractions are involved in each case.

Toluene-*p*-sulfonic acid converts the sulfoxide **229** into the thiazolidine **230**⁸⁶; a likely pathway for the reaction is outlined in Scheme 12.



SCHEME 12

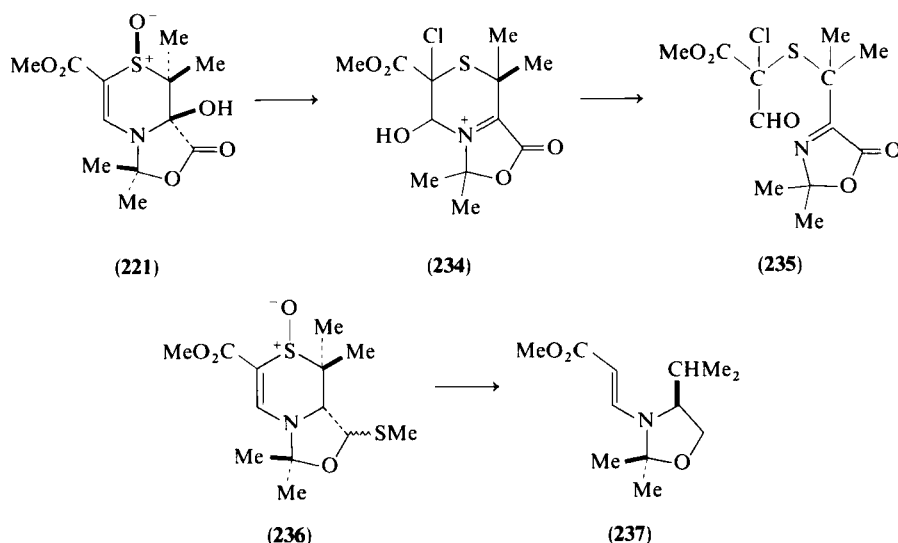
Mention has already been made of the involvement of the sulfenic acid **226** in the thermal racemization of the sulfoxide **225**, a reaction that occurred spontaneously at room temperature (Section VI,C,1,g). When heated for a few hours in boiling toluene, compounds of type **231** equilibrate with the racemates of the thiazoline oxides **233**.⁹⁸ The position of the equilibrium is dependent upon the nature of the nitrogen substituent; for example, with the isopropoxyethyl group a 3:1 mixture of derivatives **231a** and **233a** is produced, whereas with the acetyl moiety a 1:3 mixture of compounds



231b and **233b** is formed. The interconversions presumably proceed by way of the sulfenic acids **232**; evidently, these intermediates display a temperature-dependent reactivity.

c. Rupture of the Ring Skeleton

Only two reactions leading to the formation of ring-opened products have been reported for dihydrothiazine oxides. Thus when treated with acetyl chloride, the sulfoxide **221** was converted into the oxazolinone **235**, probably by way of the intermediate **234**.¹¹⁴ Raney nickel has been shown to effect the desulfurization of the compound **236**, to give the oxazolidine **237**.¹⁰²



D. PHYSICOCHEMICAL PROPERTIES

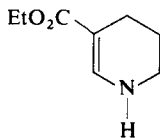
1. Infrared Spectra

The N—H stretching vibrations of 3,4-dihydro-2*H*-1,4-thiazine 1-oxides usually appear at $3100\text{--}3300\text{ cm}^{-1}$,^{79,86,101} and the C=C absorptions at $1580\text{--}1610\text{ cm}^{-1}$.^{79,86,95,98,101} Unlike the parent dihydrothiazines, the C=C bands are not significantly influenced by the attached substituents. For example, compounds **211a** and **229** show strong absorptions at 1590 and 1580 cm^{-1} , respectively. In accord with a conjugative interaction involving the nitrogen moiety, the C=O stretching vibrations of 6-methoxycarbonyl

derivatives of dihydrothiazine oxides appear at ca. 1690 cm^{-1} .^{79,95,98,101} The S^+-O^- bond is reported to absorb in the $970\text{--}1025\text{ cm}^{-1}$ region.⁸⁶

2. Ultraviolet Spectra

In contrast with the parent compounds, 3,4-dihydro-6-methoxycarbonyl-2*H*-1,4-thiazine 1-oxides show two absorption maxima at ca. 210 and 280 nm; the former band is usually less intense (ϵ ca. 7000) than the latter band (ϵ ca. 14,000).^{79,95,98,101} The long-wavelength absorption is undoubtedly the result of $n \rightarrow \pi^*$ transitions involving the $\ddot{\text{N}}\text{--C}=\text{C}(\text{CO}_2\text{Me})\text{--SO}$ chromophore. It appears that the sulfinyl group does not play an important role in the excitation, since the tetrahydropyridine **238** is reported to absorb at 286 nm (ϵ 21,000).¹¹⁷



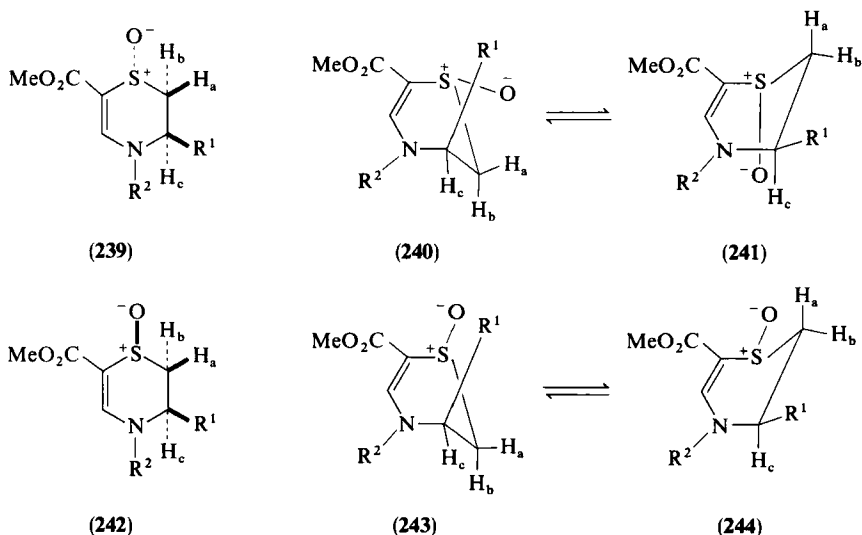
(238)

3. Nuclear Magnetic Resonance Spectra

The NMR spectra of compound **215** and several sulfoxides of types **239** and **242** have been reported and the 2-protons absorb in the δ 2.0–4.0 region.^{79,95,98,101,114} In principle, compounds of type **239** may exist as a rapidly equilibrating mixture of the conformers **240** and **241** and those of type **242** as an equilibrium mixture of the conformers **243** and **242**; in practice, the conformers **241** and **243** are overwhelmingly favored (Section VI,D,4). The proton at position 2, which is axially oriented, usually appears at significantly higher field (ca. 0.75 ppm) than its equatorial counterpart in the foregoing sulfoxides. Compared with those of the parent compounds, the 5-protons of dihydrothiazine sulfoxides show a downfield shift of 0.1–0.4 ppm (to δ 7.72–8.19); it is noteworthy that the vinylic proton of the tetrahydropyridine **238** resonates at δ 7.89.¹¹⁷ These observations suggest that the sulfur moiety slightly increases the electron density at the 5-position, compared with the sulfinyl group.

The geminal coupling constant of the 2-methylene group is dependent upon the configuration of the oxide moiety; thus (*R*)-oxides of type **239** are characterized by $J_{ab} = 12.8 - 13.6\text{ Hz}$ and (*S*)-oxides of type **242** by $J_{ab} = 14.0 - 15.2\text{ Hz}$.^{95,98,101} The vicinal coupling constants of the 2- and 3-protons

¹¹⁷ P. M. Quan and L. D. Quin, *J. Org. Chem.* **31**, 2487 (1966).



have been used to probe the conformational behavior of such molecules. For example, the conformer **241** is represented by $J_{ac} = 12.8$ Hz and $J_{bc} = 2.6$ Hz, and the conformer **243** by $J_{ac} = 2.0$ Hz and $J_{bc} = 5.0$ Hz.

4. Conformational Behavior

The conformational properties of dihydrothiazine oxides of types **239** and **242** have been examined by NMR spectroscopy.^{79,95,98,101} In the case of the (*R*)-oxides **239**, there is a dramatic preference for the conformer **241**; by contrast, the (*S*)-oxides **242** exist overwhelmingly as the conformer **243**. These results illustrate that the conformer that possesses an axial *S*-oxide is favored. The conformer **243** possesses an unfavorable 1,3-diaxial interaction between the oxide group and R^1 , and the conformer **241** is destabilized by an allylic interaction between R^1 and R^2 . Evidently, these interactions are less severe than the allylic interaction between the oxide and methoxycarbonyl groups which would be present in the conformers **244** and **240**.

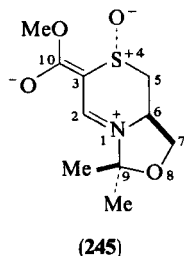
Although the stereochemistry of the sulfinyl group has not been determined, the compound **215** adopts a conformer in which the carboxy moiety is equatorial.¹¹⁵

5. Crystal Structure

The X-ray crystal structure of the sulfoxide **208a** has been determined.¹¹⁸ The atoms 1, 3, 4, 5, and 6 of the compound were found to be approximately

¹¹⁸ J. J. Guy and T. A. Hamor, *J.C.S. Perkin II*, 1132 (1974).

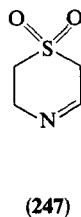
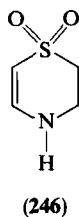
coplanar and, in accord with a significant contribution from the canonical form **245** to the ground-state electronic configuration, the N1—C2 bond was much shorter (131.6 pm), the C2—C3 bond was longer (139 pm), and the C3—C10 bond was shorter (144.9 pm) than the normal values.



VII. Dihydro-1,4-thiazine 1,1-Dioxides

A. TAUTOMERIC BEHAVIOR

In principle, dihydro-1,4-thiazine 1,1-dioxide may exist as the tautomer **246** or **247**; only derivatives of the former compound have been reported.

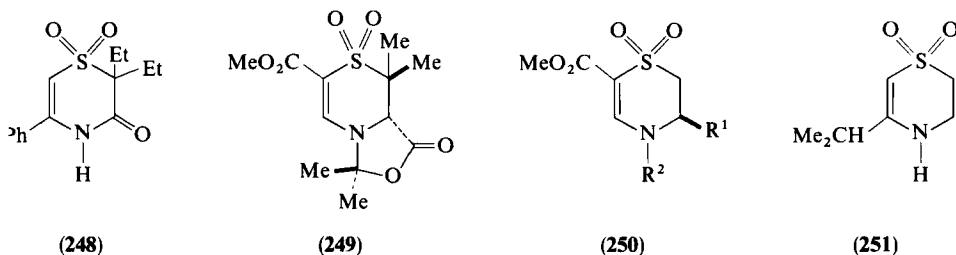


B. SYNTHESIS

1. Oxidation of Dihydrothiazines and Dihydrothiazine Oxides

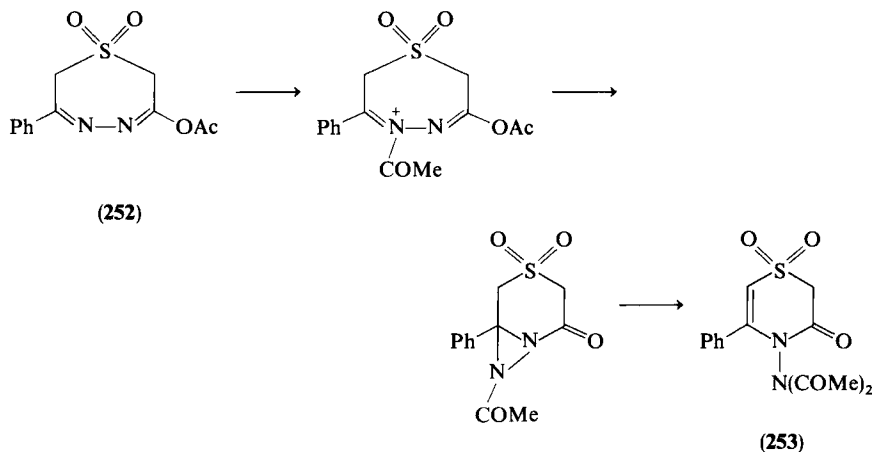
Peracids are the normal reagents for effecting the conversions of dihydrothiazines and their oxides into dihydrothiazine dioxides. Thus the compound **82** was transformed into the sulfone **248** by peracetic acid⁶¹ and the sulfoxide **219** afforded the derivative **249** when treated with *m*-chloroperbenzoic acid.⁹⁵ Unpublished studies, performed in the author's laboratory, have shown that compounds of type **199** are readily converted into the sulfones **250** by *m*-chloroperbenzoic acid.²⁴ In one instance, oxygen has been reported to act

as the oxidant; thus the sulfone **251** was formed when the parent dihydrothiazine was exposed to the air in acetone solution.⁴⁴



2. Isomerization of Thiadiazepine Dioxides

When treated with hot acetic anhydride, the thiadiazepine dioxide **252** was transformed into the dihydrothiazinone dioxide **253**; a possible pathway for the rearrangement is suggested in Scheme 13.¹¹⁹

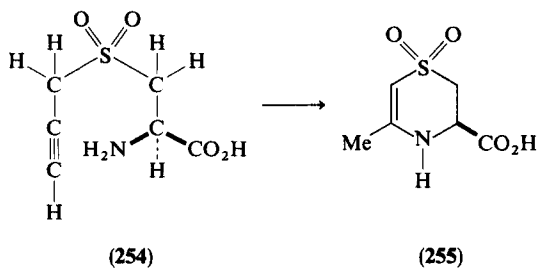


SCHEME 13

3. Cyclization of Acyclic Precursors

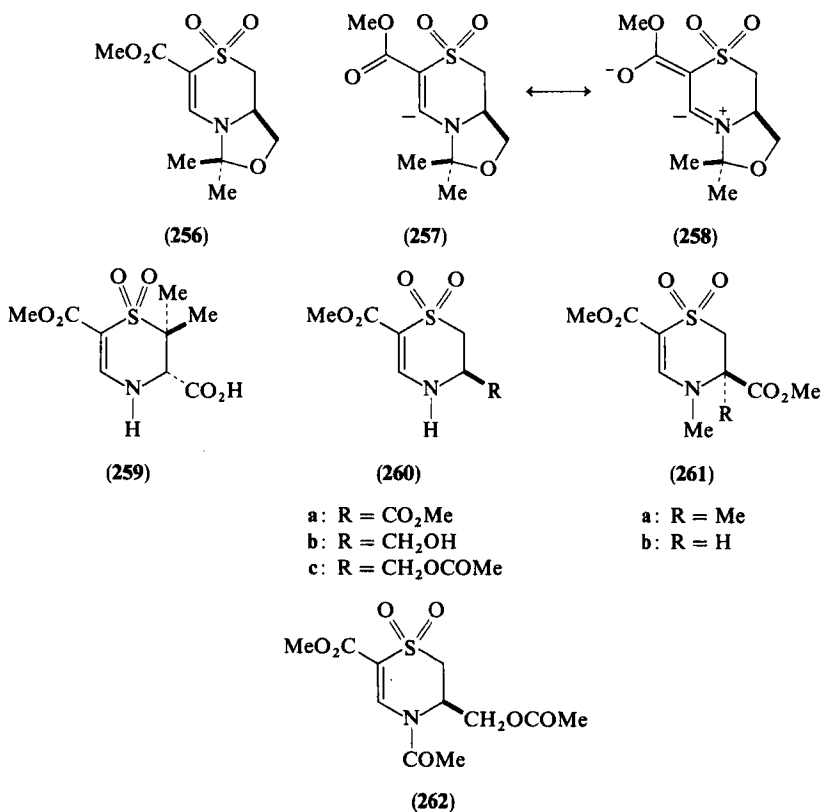
The only example in which the dihydrothiazine dioxide ring has been constructed by the cyclization of an acyclic precursor is provided by the ammonia-induced conversion of the sulfone **254** into compound **255**.¹¹⁵

¹¹⁹ I. Sataty, *Tetrahedron* **28**, 2307 (1972).



C. REACTIVITY

As expected, the hydrogen atoms adjacent to the sulfonyl group of the compound **256** undergo exchange in the presence of potassium *t*-butoxide and $[^2\text{H}_6]$ dimethyl sulfoxide; no selectivity is observed. Deuterium exchange of the vinylic hydrogen atom also occurs, indicating that the vinyl anion



257 is a readily accessible species; presumably, the structure **258** contributes to its stabilization²⁴ (Section VI,C,1,e).

When treated with sodium hydroxide, the compound **249** was converted into the racemate of the acid **259**; evidently, the starting material underwent complete racemization prior to hydrolysis.²⁴ A comparison of this behavior with that observed for the derivatives **132a** and **219** (Sections V,C,1,e and VI,C,1,d) is in accord with the expected increase in acidity of the oxazolidinone protons in the series **132a**, **219**, and **249**. Evidence for the acidity of the 3-proton of the derivative **260a** is provided by the formation of the product **261a**, as a racemate, in the presence of methyl iodide and potassium carbonate.²⁴ In contrast with the alcohol **109c**, which undergoes exclusive *O*-acetylation, the compound **260b** was transformed into **262** by acetic anhydride and pyridine.²⁴

D. PHYSICOCHEMICAL PROPERTIES

1. *Infrared Spectra*

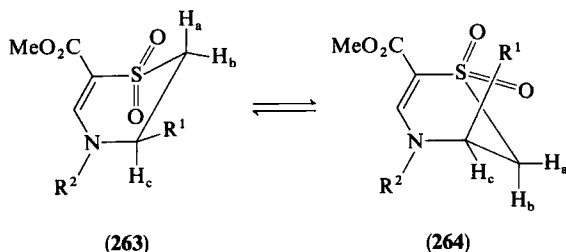
The C=C absorptions of 3,4-dihydro-2*H*-1,4-thiazine 1,1-dioxides are observed in the 1585–1610 cm⁻¹ region.^{24,95} In accord with a conjugative interaction involving the nitrogen moiety, the C=O stretching vibrations of 6-methoxycarbonyl derivatives appear in the 1690–1710 cm⁻¹ region.^{24,95}

2. *Ultraviolet Spectra*

The UV spectra of 3,4-dihydro-6-methoxycarbonyl-2*H*-1,4-thiazine 1,1-dioxides are very similar to those of the corresponding sulfoxides (Section VI,D,2).^{24,95} Two absorption maxima are observed: a band at ca. 205 nm (ϵ ca. 3000) and a band at ca. 270 nm (ϵ ca. 13,000). The latter absorption is due to $n \rightarrow \pi^*$ transitions involving the $\ddot{N}-C=C(CO_2Me)-SO_2$ chromophore.

3. *Nuclear Magnetic Resonance Spectra*

The 2-protons of dihydrothiazine dioxides, e.g., **255** and compounds of type **250**, absorb in the δ 2.7–4.0 region²⁴; as expected, those of the derivative **253** resonate at significantly lower field (δ 4.49).¹¹⁹ The 5-protons of dihydrothiazine dioxides of type **250** usually appear in the δ 7.6–7.9 region.²⁴ In the case of the derivatives **253**¹¹⁹ and **255**,¹¹⁵ the 6-protons resonate at δ 6.38 and δ 4.81, respectively.



The protons at position 2 of dihydrothiazine dioxides possess a geminal coupling constant of $J_{ab} = 13.0\text{--}14.6$ Hz.^{24,115} The vicinal coupling constants of the 2- and 3-protons have been used to probe the conformational behavior of such molecules.²⁴ Thus, the conformer **263**, exemplified by compound **256**, is characterized by $J_{ac} = 13.0$ Hz and $J_{bc} = 3.0$ Hz, and the conformer **264** by $J_{ac} = 3.2$ Hz and $J_{bc} = 4.0$ Hz. In the case of the sulfone **253**, long-range coupling ($J = 1.4$ Hz) is observed between the 2- and 6-protons¹¹⁹; a similar effect is noted with compound **255**, although the coupling constant is somewhat larger ($J = 3.0$ Hz).¹¹⁵

4. Conformational Behavior

The conformational properties of dihydrothiazine dioxides of type **250** have been examined by NMR spectroscopy.²⁴ In general, *N*-unsubstituted derivatives, e.g., **260a–c**, exist as a 1:1–3:1 mixture of the conformers **263** and **264**. By contrast, *N*-substituted compounds, e.g. **261b** and **262**, favor the conformer **264**. The conformer **263** is destabilized by an allylic interaction between R¹ and R², whereas the conformer **264** possesses an unfavorable 1,3-diaxial interaction between an oxide group and R¹. Evidently, the latter interaction is less severe than the former when R¹ and R² are groups other than hydrogen atoms.

Compound **255** adopts the conformer in which the carboxy moiety is equatorial.¹¹⁵

VIII. Conclusion

It is now more than 30 years since the first monocyclic 1,4-thiazine was described; nevertheless, the chemistry of such compounds is still relatively undeveloped. The 1,4-thiazine ring is of importance in nature where, in fusion with the benzene ring, it is found in the trichochrome pigments. It is also a structural feature of the phenothiazines, synthetic compounds that are of considerable medicinal value. Furthermore, 1,4-thiazines are of in-

trinsic interest because of their tautomeric possibilities, their opportunities for intramolecular and intermolecular cycloadditions, and their potential utility in synthesis. On these counts, a further study of 1,4-thiazines would appear to be warranted.

By contrast, the chemistry of dihydro-1,4-thiazines is in a much healthier state. The abundance of syntheses, particularly for the derivation of the 3,4-dihydro tautomers, is in large measure responsible for this situation. It is clear that dihydrothiazines possess some interesting and unusual patterns of reactivity, particularly in their ability to undergo molecular rearrangements, which are of general organic chemical interest. It is also apparent that such compounds are versatile precursors of both known and rare heterocyclic systems.

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Recent Advances in Pyridazine Chemistry

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I. Introduction

Since our last review of pyridazines¹ major advances in the chemistry of this heterocyclic system have been made. The two main reasons for the many publications in the past decade, exceeding those reported up to 1966, are first, theoretical interest, and second, the continuing search for biologically active compounds. This report covers the literature to November 1977.

¹ M. Tišler and B. Stanovnik, *Adv. Heterocycl. Chem.* **9**, 211 (1968).

In the meantime, several reviews of the chemistry of heterocyclic compounds appeared that in part cover aspects of pyridazine chemistry. They include syntheses and reactivity of pyridazinones and pyridazines,² electrophilic substitutions on pyridazines,³ conversion of pyridazines to other compounds,⁴⁻⁶ photochemistry of N-oxides,⁷ hindered rotation in reduced acylpyridazines⁸ and azidotetrazolo isomerizations.⁹

Until recently pyridazines had not been found in nature; it was believed that microorganisms do not generate hydrazine or diimide, necessary for building up the pyridazine skeleton. However, Hassall and co-workers have now isolated from *Streptomyces jamaicensis* antibacterial monamycins,¹⁰ which are cyclohexadepsipeptides and contain as structural unit hexahydro-pyridazine-3-carboxylic acid or its substituted derivatives.¹¹⁻¹³

II. Synthetic Methods

A. FROM CARBONYL COMPOUNDS, ACIDS, LACTONES, ANHYDRIDES, AND RELATED COMPOUNDS

The standard synthesis of pyridazines from γ -keto acids or esters has been applied to the preparation of many derivatives.¹⁴⁻²⁹

² T. Terai, *Yuki Gosei Kagaku Kyokai Shi* **27**, 74 (1969) [*CA* **70**, 87607 (1969)].

³ Zh. I. Akselrod and V. M. Berezovskii, *Usp. Khim.* **39**, 1337 (1970).

⁴ H. Igeta, *Yuki Gosei Kagaku Kyokai Shi* **31**, 867 (1973).

⁵ A. Karklina, *Biol. Ak. Savienojumu Kim. Technol. Rigas Politech. Inst.* **1**, 86 (1974).

⁶ S. Yurugi, *Takeda Kenkyusho Ho* **34**, 53 (1975).

⁷ F. Bellamy and J. Streith, *Heterocycles* **4**, 1391 (1976).

⁸ W. E. Stewart and T. H. Siddall, *Chem. Rev.* **70**, 517 (1970).

⁹ M. Tišler, *Synthesis*, 123 (1973).

¹⁰ C. H. Hassall, R. B. Morton, Y. Ogihara, and D. A. S. Phillips, *J. Chem. Soc. C*, 526 (1971).

¹¹ K. Bevan, J. S. Davies, C. H. Hassall, R. B. Morton, and D. A. S. Phillips, *J. Chem. Soc. C*, 514 (1971).

¹² C. H. Hassall, R. B. Morton, Y. Ogihara, and W. A. Thomas, *Chem. Commun.*, 1079 (1969).

¹³ C. H. Hassall, Y. Ogihara, and W. A. Thomas, *J. Chem. Soc. C*, 522 (1971).

¹⁴ S. Agbalyan, G. V. Grigoryan, A. A. Dzaninyan, and K. G. Oganessian, *Arm. Khim. Zh.* **27**, 139 (1974) [*CA* **81**, 37527 (1974)].

¹⁵ S. G. Agbalyan, G. V. Grigoryan, and A. A. Dzaninyan, *Khim. Geterotsikl. Soedin.*, 1079 (1974).

¹⁶ S. G. Agbalyan, G. A. Galoyan, and G. V. Grigoryan, *Arm. Khim. Zh.* **27**, 673 (1974) [*CA* **82**, 16765 (1975)].

¹⁷ W. V. Curran and A. Ross, *J. Med. Chem.* **17**, 273 (1974).

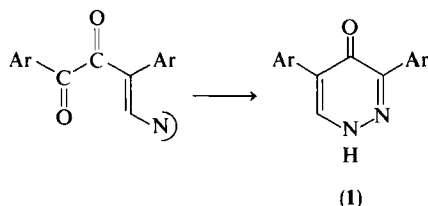
¹⁸ R. Dabard and M. Le Plouzennec, *C.R. Acad. Sci., Ser. C*, **268**, 290 (1969).

¹⁹ S. Eskola, E. Bernström, P. Erke, M. Kokko, M. Raunu, and E. Wartiovaara, *Suom. Kemistil. B* **42**, 233 (1969) [*CA* **71**, 6131 g (1969)].

²⁰ A. Exinger and C. G. Wermuth, *Synthesis*, 817 (1974).

²¹ A. K. Fateen, A. M. Sammour, and M. F. Ismail, *J. Chem. U.A.R.* **10**, 321 (1967).

Pyridazine syntheses from unsaturated 1,4-diketones have been applied in several new ways.³⁰⁻³⁷ The reaction with hydrazines is usually performed in the presence of mineral acid; otherwise *N*-aminopyrroles may be formed.^{31,32} Some saturated 1,4-diketones are claimed to react with hydrazines to give pyridazines.³⁸⁻⁴² Instead of 1,4-dicarbonyl compounds, 1,4-enaminoketones were employed.⁴³ So far, this synthetic approach is limited to the preparation of 3,5-diaryl-4(1H)-pyridazinones (I). In the



above cyclizations *cis*-isomers are preferable as illustrated by 3-hexene-2,5-dione. The *cis*-isomer reacted readily to give 3,5-dimethylpyridazine, whereas the *trans*-isomer gave the same pyridazine in lower yield accompanied by about the same amount of three other compounds, one identified as 4-hydroxy-4-methyl-2-pentanone.⁴⁴

²² A. K. Fateen, S. M. A. R. Omaran, A. M. Kaddah, and A. H. Moustafa, *Indian J. Chem.* **14B**, 276 (1976).

²³ A. K. Fateen, S. A. R. Omran, N. Shams, and A. M. Kaddah, *Indian J. Chem.* **14B**, 99 (1976).

²⁴ A. N. Kost, M. A. Yurovskaya, and Nguyen Min Thao, *Khim. Geterotsikl. Soedin.*, 1512 (1975).

²⁵ A. Sammour and M. Elhashash, *J. Prakt. Chem.* **314**, 906 (1972).

²⁶ A. A. Ponomarev and V. A. Sedavkina, *Metody Poluch. Khim. Reaktivov Prep.* **29**, (1967) [*CA* **71**, 30431 (1969)].

²⁷ E. A. Steck, R. P. Brundage, and L. T. Fletcher, *J. Heterocycl. Chem.* **11**, 755 (1974).

²⁸ C. G. Wermuth and A. Exinger, *Agressologie* **13**, 285 (1972).

²⁹ G. Westphal, *Z. Chem.* **9**, 339 (1969).

³⁰ W. Ried and R. Lantzsch, *Justus Liebigs Ann. Chem.* **750**, 97 (1971).

³¹ G. Rio, and A. Lecas-Nawrocka, *Bull. Soc. Chim. Fr.*, 1723 (1971).

³² G. Rio and A. Lecas-Nawrocka, *Bull. Soc. Chim. Fr.*, 2824 (1974).

³³ M. I. Shevchuk, A. F. Tolochko, and A. V. Dombrovskii, *Zh. Org. Khim.* **6**, 1108 (1970).

³⁴ M. I. Shevchuk, A. F. Tolochko, and A. V. Dombrovskii, *Zh. Org. Khim.* **7**, 1692 (1971).

³⁵ J. C. Trisler, J. K. Doty, and J. M. Robinson, *J. Org. Chem.* **34**, 3421 (1969).

³⁶ H. Saikachi and J. Matsuo, *Yakugaku Zasshi* **89**, 1622 (1969) [*CA* **72**, 55118 (1970)].

³⁷ K. N. Zelenin and I. P. Bezhan, *Dokl. Akad. Nauk SSSR* **191**, 1292 (1970).

³⁸ F. Schon, L. Jung, and P. Cordier, *C.R. Acad. Sci., Ser. C*, **267**, 490 (1968).

³⁹ K. N. Zelenin and Yu. Ya. Dumpis, *Zh. Org. Khim.* **6**, 1349 (1970).

⁴⁰ K. N. Zelenin and Yu. Ya. Dumpis, *Khim. Geterotsikl. Soedin.*, 400 (1971).

⁴¹ K. N. Zelenin and Yu. Ya. Dumpis, *Khim. Geterotsikl. Soedin.*, 1566 (1971).

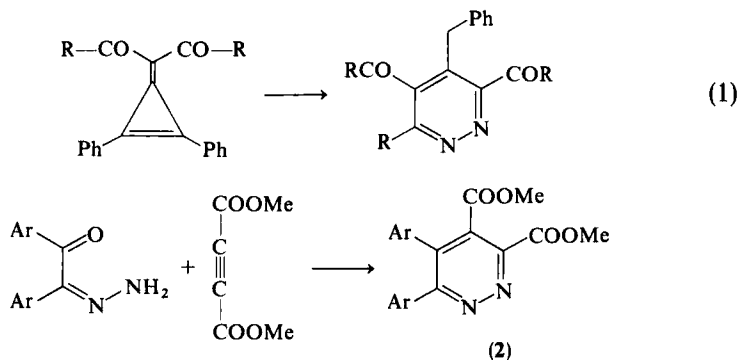
⁴² K. N. Zelenin and Yu. Ya. Dumpis, *Zh. Org. Khim.* **9**, 1295 (1973).

⁴³ R. F. Abdulla, *Tetrahedron Lett.*, 521 (1976).

⁴⁴ J. A. Hirsch and H. J. Szur, *J. Heterocycl. Chem.* **9**, 523 (1972).

The reaction between some 1,4-diketones and 2,4-dinitrophenylhydrazine has been reinvestigated: a mixture of bishydrazones and the corresponding *N*-(2,4-dinitroanilino)(pyrroles is formed. With diethyl α,α' -diacetylsuccinate, in addition, a pyridazine derivative was formed.⁴⁵

In other related syntheses, pyridazines were formed from 1,2-diphenyl-3-(diacylmethylene)cyclopropenes, as shown in Eq. (1)⁴⁶ or from *trans*-1,2-dibenzoyl-3,3-diphenylcyclopropane.⁴⁷ Similarly, pyridazines are formed from hydrazines or semicarbazide and γ -trichloromethyl- α,β -unsaturated ketones.⁴⁸⁻⁵² Pyridazines may also be obtained from 1,2-diketones. The reaction between benzoin and hydrazine was investigated in detail. A complex mixture of various compounds is formed, among them 3,4,5,6-tetraphenylpyridazine in low yield.⁵³ Benzil monohydrazones and analogs when treated with vinyltriphenylphosphonium bromide also give 2,3-dihydropyridazines in moderate yield.^{54,55} Benzil monohydrazone and related compounds react with dimethyl acetylenedicarboxylate to give a mixture of the corresponding ketazine, basketazine, and pyridazine 2.⁵⁶ The last is the main product in the absence of solvent.



⁴⁵ T. D. Binns and R. Brettell, *J. Chem. Soc. C*, 341 (1966).

⁴⁶ S. S. Hecht, *Tetrahedron Lett.*, 3731 (1972).

⁴⁷ R. M. White and M. A. Battiste, *J. Org. Chem.* **41**, 1245 (1976).

⁴⁸ F. DeChamps de Saint Leger, *Ann. Chim. (Paris)*, 411 (1972).

⁴⁹ Y. Y. Lee, W. Y. Lee, and S. H. Chang, *Daehan Hwahak Hwojee* **14**, 61 (1970) [*CA* **73**, 77176 (1970)].

⁵⁰ Y. Y. Lee, *Daehan Hwahak Hwojee* **16**, 189 (1972) [*CA* **77**, 139947 (1972)].

⁵¹ Y. Y. Lee, W. Y. Lee, and S. H. Chang, *Daehan Hwahak Hwojee* **16**, 299 (1972) [*CA* **77**, 152095 (1972)].

⁵² Y. Y. Lee and S. Z. Song, *Daehan Hwahak Hwojee* **17**, 25 (1973) [*CA* **79**, 53244 (1973)].

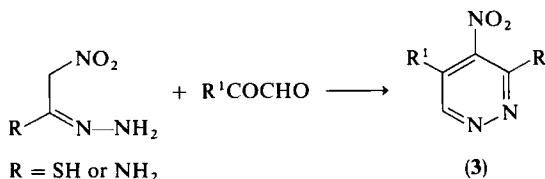
⁵³ A. M. Comrie, *J. Chem. Soc. C*, 2807 (1971).

⁵⁴ E. E. Schweizer and C. M. Kopay, *J. Org. Chem.* **37**, 1561 (1972).

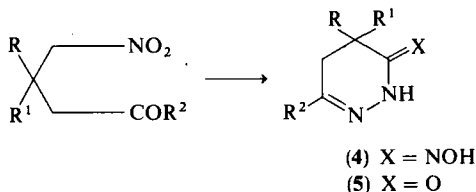
⁵⁵ E. E. Schweizer, C. S. Kim, C. S. Labaw, and W. P. Murray, *Chem. Commun.*, 7 (1973).

⁵⁶ R. K. Gupta and M. V. George, *Indian J. Chem.* **10**, 875 (1972).

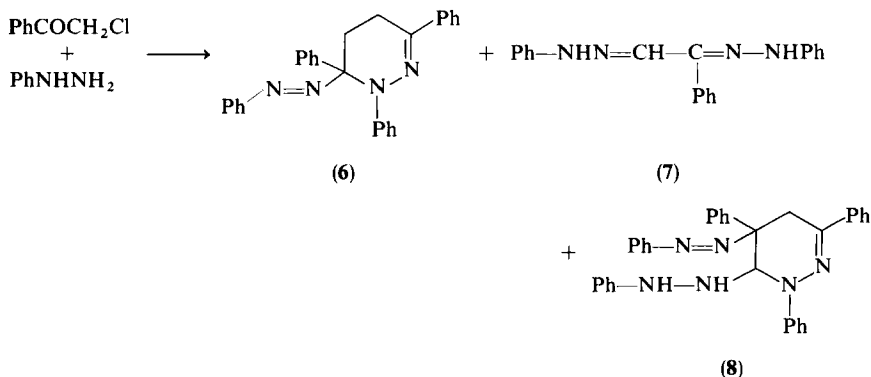
A new synthetic approach to 4-nitropyridazines has been developed recently. The hydrazide of nitrothioacetic acid, or the corresponding amidrazone, reacts with glyoxal or methylglyoxal under base-catalyzed conditions to give **3**.⁵⁷



Several other ketones were employed as starting material. Pyridazines were obtained from γ -nitroketones and hydrazine. The initially formed 4,5-dihydro-3(2H)-pyridazinone oximes (**4**) are transformed with dilute acid into **5**.⁵⁸ The reaction is postulated to proceed via a nitrile oxide, generated from the nitromethyl group.



The reaction between phenacyl chloride and phenylhydrazine on reinvestigation was shown to give a mixture of three products (**6**–**8**).⁵⁹ Compound **8** is formed very slowly.

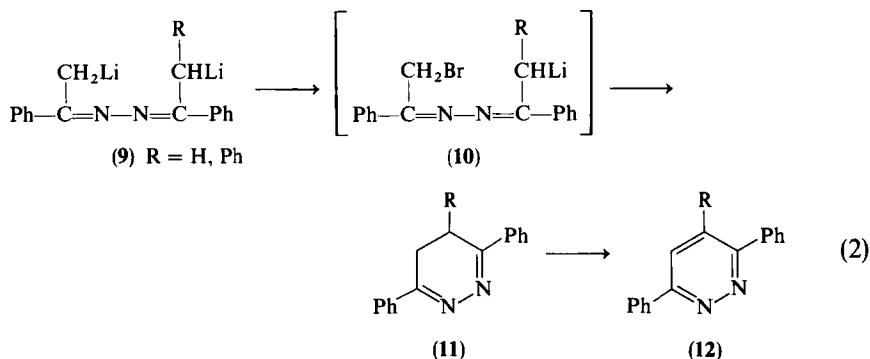


⁵⁷ H. Hamberger, H. Reinshagen, G. Schulz, and G. Sigmund, *Tetrahedron Lett.*, 3619 (1977).

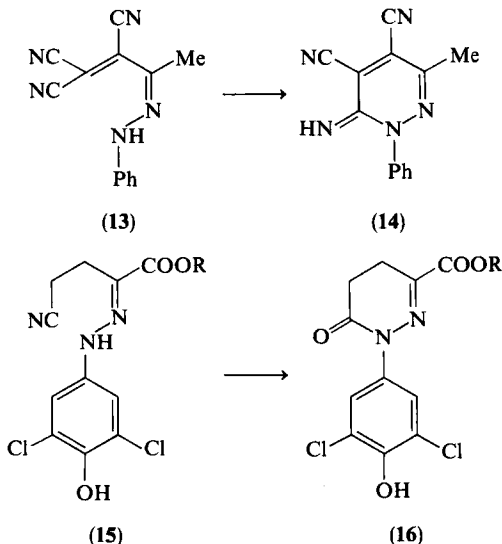
⁵⁸ W. Mack, *Chem. Ber.* **109**, 3564 (1976).

⁵⁹ W. C. Stickler and W. Hoffman, *Angew. Chem.* **82**, 254 (1970).

Pyridazines were prepared from a variety of hydrazones or azines. 3,6-Di- or 3,4,6-triphenylpyridazine were prepared from acetophenone hydrazone and deoxybenzoin [Eq. (2)]. The azine was first converted into



the 1,6-dilithio salt **9** and then cyclized with 2,3-dibromo-2,3-dimethylbutane to **11**, most probably via the bromo lithio salt **10**. Hydrogen peroxide oxidation gave the fully aromatic pyridazines (**12**).⁶⁰ Lithiated hydrazones may also be condensed with diethyl oxalate and then cyclized to pyridazines.⁶¹ In other reactions, ω -bromoacetophenone semicarbazone reacts with

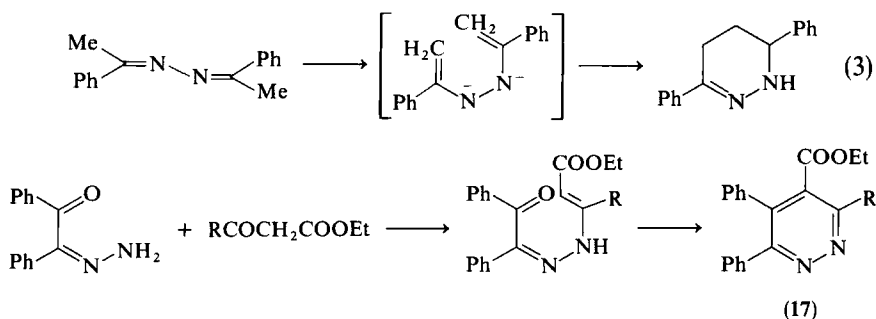


⁶⁰ F. E. Henoch, K. G. Hampton, and C. R. Hauser, *J. Am. Chem. Soc.* **91**, 676 (1969).

⁶¹ R. M. Sandifer, L. W. Dasher, W. M. Hollinger, C. W. Thomas, D. C. Reames, C. F. Beam, R. S. Foote, and C. R. Hauser, *J. Heterocycl. Chem.* **12**, 1159 (1975).

enamines to give 1,4-dihydropyridazines,⁶² and the tricyano hydrazone **13** obtained from cyanoacetone phenylhydrazone and tetracyanoethylene is transformed upon heating into the pyridazine derivative **14**.⁶³ In an attempted Fischer indole synthesis from the hydrazone **15**, the tetrahydropyridazinone **16** was obtained.⁶⁴ Perchlorovinylacetaldehyde reacts with hydrazines to give 4,5-dichloropyridazin-6-ones.⁶⁵

Examples of pyridazine synthesis from azines involve reaction between tetrafluoroformaldazine and perfluorosuccinyl fluoride in the presence of cesium fluoride to give a perfluoropyridazine,⁶⁶ or *via* ketazine anions, as for acetophenone azine [Eq. (3)].⁶⁷ The azine from benzyl monohydrazone and ethyl acetoacetate or benzoylacetate is cyclized under basic conditions into the pyridazine **17**.⁶⁸



The reaction between substituted maleic anhydrides and hydrazines is a well-traveled route for the synthesis of many pyridazinones.⁶⁹⁻⁷⁶ Hydrazines with a strong electron-donor group form pyridazinones directly; others give

⁶² V. Sprio and S. Plescia, *Ann. Chim. (Rome)* **62**, 345 (1972).

⁶³ H. Junek, A. Hermetter, and H. Fischer-Colbrie, *Chem. Ber.* **109**, 1787 (1976).

⁶⁴ W. Ried and E. A. Baubach, *Justus Liebigs Ann. Chem.* **726**, 81 (1969).

⁶⁵ A. Roedig and W. Wenzel, *Justus Liebigs Ann. Chem.* **728**, 1 (1969).

⁶⁶ P. H. Ogden, *J. Chem. Soc. C*, 2920 (1971).

⁶⁷ Z. Yoshida, T. Harada, and Y. Tamaru, *Tetrahedron Lett.*, 3823 (1976).

⁶⁸ S. Evans and E. E. Schweizer, *J. Org. Chem.* **42**, 2321 (1977).

⁶⁹ M. Augustin and P. Reinemann, *Z. Chem.* **13**, 12 (1973).

⁷⁰ M. Augustin and P. Reinemann, *Z. Chem.* **13**, 214 (1973).

⁷¹ R. W. H. Berry and A. Burawoy, *J. Chem. Soc. C*, 1316 (1970).

⁷² P. Condorelli, G. Pappalardo, and M. Raspagliesi, *Boll. Sedute Accad. Gioenia Sci. Nat. Catania* **9**, 242 (1967) [*CA* **71**, 70556 (1969)].

⁷³ T. Maki and M. Takaya, *Yuki Gosei Kagaku Kyokai Shi* **28**, 462 (1970) [*CA* **73**, 14789 (1970)].

⁷⁴ K. C. Liu and H. J. Jan, *J. Chin. Chem. Soc. (Taipei)* **22**, 243 (1975).

⁷⁵ M. Parnarouskis and H. Rubinstein, *J. Heterocycl. Chem.* **13**, 423 (1976).

⁷⁶ H. Reimlinger, J. J. M. Vandewalle, and W. R. F. Lingier, *Chem. Ber.* **103**, 1960 (1970).

the corresponding 3-carboxyacryloylhydrazines. Sterically hindered hydrazines, for example α -cumylhydrazine, give only the maleamic acid.⁷⁷ These 3-carboxyacryloylhydrazines, when dehydrated in acid media, give either aminomaleimides or pyridazinones. If the hydrazine residue is substituted with an electron-donor group the formation of pyridazinone is favored or the initially formed maleimide is isomerized under the influence of the acid into the pyridazinone.⁷⁸⁻⁹¹ A chemical differentiation between an *N*-aminoimide or cyclic hydrazide is based upon the reaction with lead tetraacetate: only *N*-aminoimides form nitrenes, which are trapped in dimethyl sulfoxide to give the corresponding *S,S*-dimethyl sulfoximides.⁹²

The extensively used synthesis of pyridazines from 3-formylacrylic acids or esters has been extended to many new products.⁹³⁻⁹⁷ Mucochloric acid and hydrazine give compound **18** directly or as a by-product; on hydrolysis with dilute alkali, **18** gives **19**.⁹⁸ Transformations of some nitrophenylhydrazides of maleic acid into nitrophenylaminomaleimides or pyridazines were studied.^{78,79}

A new synthesis of 1,2-disubstituted perhydropyridazine-3,6-diones has been developed. Succinic anhydride or 3-carbomethoxypropionyl chloride,

⁷⁷ W. H. Pirkle and P. L. Gravel, *J. Org. Chem.* **42**, 296 (1977).

⁷⁸ S. Baloniak, *Rocz. Chem.* **41**, 1143 (1967).

⁷⁹ S. Baloniak, *Rocz. Chem.* **42**, 1231 (1968).

⁸⁰ S. Baloniak, *Rocz. Chem.* **42**, 1867 (1968).

⁸¹ S. Baloniak, *Rocz. Chem.* **43**, 315 (1969).

⁸² S. Baloniak, *Rocz. Chem.* **43**, 1187 (1969).

⁸³ S. Baloniak and A. Mroczkiewicz, *Rocz. Chem.* **44**, 441 (1970).

⁸⁴ S. Baloniak and U. Wrzeciono, *Rocz. Chem.* **45**, 567 (1971).

⁸⁵ S. Baloniak and A. Mroczkiewicz, *Rocz. Chem.* **48**, 399 (1974).

⁸⁶ S. Baloniak and A. Mroczkiewicz, *Rocz. Chem.* **48**, 1623 (1974).

⁸⁷ S. Baloniak, *Rocz. Chem.* **46**, 751 (1972).

⁸⁸ S. Baloniak, U. Thiel, and M. Pacholczyk, *Acta Pol. Pharm.* **33**, 73 (1976).

⁸⁹ A. Le Berre, J. Godin, and R. Garreau, *C.R. Acad. Sci., Ser. C*, **265**, 570 (1967).

⁹⁰ H. Rubinstein, J. E. Skarbek, and H. Feuer, *J. Org. Chem.* **36**, 3372 (1971).

⁹¹ H. Rubinstein, M. Parnarouskis, and H. Feuer, *J. Org. Chem.* **38**, 2166 (1973).

⁹² B. Stanovnik and M. Tišler, *Org. Prep. Proced. Int.* **5**, 87 (1973).

⁹³ L. Ya. Avota, V. Egerts, T. I. Tikhvinskaya, and S. A. Giller, *Latv. PSR Zinat. Akad. Vestis, Khim. Ser.*, 272 (1976) [*CA* **85**, 123844 (1976)].

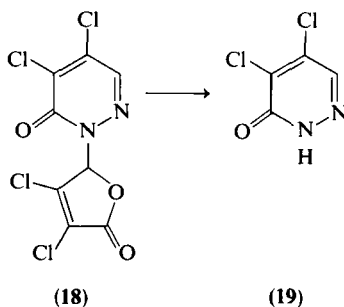
⁹⁴ S. A. Giller, L. Ya. Avota, and N. Ya. Ozolin, *Latv. PSR Zinat. Akad. Vestis, Khim. Ser.* **348** (1968).

⁹⁵ A. H. Karklina, E. Yu. Gudriniece, and J. Paulins, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, 496 (1972) [*CA* **77**, 139948 (1972)].

⁹⁶ B. Krawczynska and Z. Eckstein, *Przem. Chem.* **52**, 276 (1973).

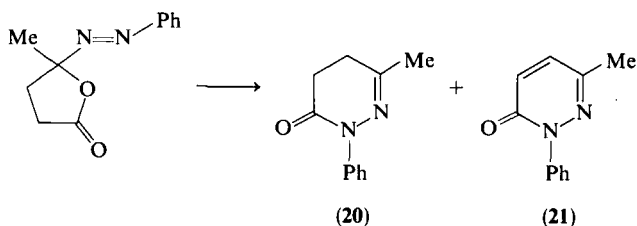
⁹⁷ G. S. Predvoditeleva, T. V. Kartseva, and M. N. Shchukina, *Khim.-Farm. Zh.* **6**, 11 (1972).

⁹⁸ J. K. Landquist and S. E. Meek, *Chem. Ind.* (London), 688 (1970).



when treated with 1,2-disubstituted hydrazines, give the corresponding carboxypropionylhydrazides, which are subsequently converted thermally or in the presence of polyphosphoric acid or thionyl chloride into perhydropyridazine-3,6-diones.⁹⁹ These can be reduced with diborane to 1,2-disubstituted perhydropyridazines.¹⁰⁰

Some lactones serve as starting material. γ -Phenylazo- γ -valerolactone is thermally rearranged to a mixture of pyridazinones **20** and **21** in a ratio of 1.75:1.¹⁰¹ A complex mechanism is proposed. Pyridazines also result from hydrazines and substituted γ -lactones^{102,103} or β -acyl- γ -lactones, which react as 1,4-dicarbonyl compounds.¹⁰⁴ γ -Chloroketones react with substituted hydrazines to give pyridazines or *N*-aminopyrrolines, depending upon the hydrazine used.¹⁰⁵ γ -Chlorobutanal gives the corresponding 1,4,5,6-tetrahydropyridazine.¹⁰⁶



⁹⁹ H. Feuer, E. P. Rosenquist, and F. Brown, *Isr. J. Chem.* **6**, 587 (1968).

¹⁰⁰ H. Feuer and F. Brown, *J. Org. Chem.* **35**, 1468 (1970).

¹⁰¹ H. Lui and J. Warkentin, *Can. J. Chem.* **50**, 1967 (1972).

¹⁰² W. I. Awad, S. M. A. Omran, and A. I. Hashem, *J. Chem. U.A.R.* **10**, 287 (1967) [*CA* **69**, 86677 (1968)].

¹⁰³ W. I. Awad, A. I. Hashem, and K. El-Badry, *Indian J. Chem.* **13**, 1139 (1975).

¹⁰⁴ H. Wamhoff and F. Korte, *Justus Liebigs Ann. Chem.* **724**, 217 (1969).

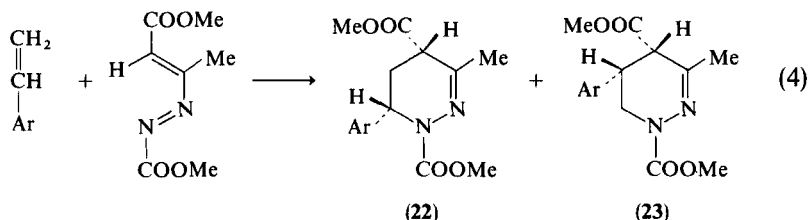
¹⁰⁵ I. I. Grandberg and N. M. Przhivalskii, *Khim. Geterotsikl. Soedin.*, 1273 (1970).

¹⁰⁶ K. N. Zelenin and V. G. Kamerdinerov, *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.* **12**, 911 (1969).

B. APPLICATION OF CYCLOADDITION REACTIONS

Cycloaddition reactions form efficient syntheses for many heterocyclic systems, and several extensive reviews on this subject have appeared. In the last decade many such reactions have been used for the synthesis of pyridazines.

The (4+2)-cycloaddition reactions are theoretically and experimentally well founded for electron-rich dienes. However, those reactions with electron-rich dienophiles are less investigated. An early application of the "inverse" type of (4+2)-cycloaddition to pyridazine synthesis, i.e., from electron-deficient azoalkenes and alkenes, was reported by Sommer in 1977, [Eq. (4)]. A mixture of regioisomeric products **22** and **23** was obtained.^{107,108} However, in the presence of diphenylketene, products of either (2+2)- and/or (4+2)-cycloaddition (i.e., pyridazines) are formed; arylazoalkenes thus behave similarly to α,β -unsaturated carbonyl compounds in cycloadditions.¹⁰⁹ 2-Phenylazo-1-alkenes dimerize (a (4+2)-cycloaddition) in the absence of solvent to give pyridazines, or they may react with dienophiles.¹¹⁰⁻¹¹⁵ Some other cycloadditions of this type are reported.¹¹⁶⁻¹²⁰



The tetraphenyl ester of azodiphosphonic acid is a more reactive dienophile than diethyl azodicarboxylate. Because of its instability it is prepared from

¹⁰⁷ S. Sommer, *Tetrahedron Lett.*, 117 (1977).

¹⁰⁸ S. Sommer, *Chem. Lett.*, 583 (1977).

¹⁰⁹ S. Sommer, *Angew. Chem.* **89**, 59 (1977).

¹¹⁰ J. Schantl, *Monatsh. Chem.* **103**, 1705 (1972).

¹¹¹ J. Schantl, *Monatsh. Chem.* **105**, 220 (1974).

¹¹² J. Schantl, *Monatsh. Chem.* **105**, 229 (1974).

¹¹³ J. Schantl, *Monatsh. Chem.* **105**, 314 (1974).

¹¹⁴ J. Schantl, *Monatsh. Chem.* **105**, 322 (1974).

¹¹⁵ J. Schantl, *Z. Naturforsch., Teil B* **32**, 72 (1977).

¹¹⁶ K. N. Zelenin, and Z. M. Matveeva, *Dokl. Akad. Nauk SSSR* **184**, 1105 (1969).

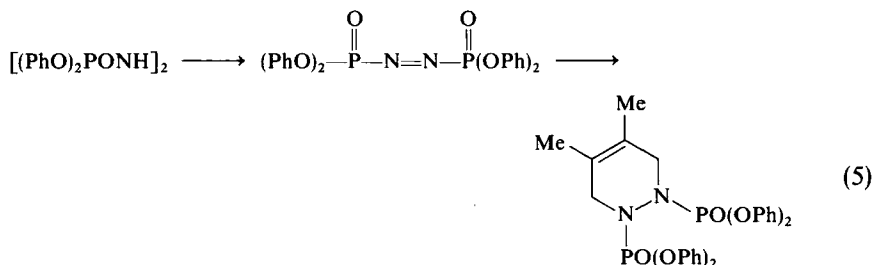
¹¹⁷ K. N. Zelenin and Z. M. Matveeva, *Zh. Org. Khim.* **4**, 532 (1968).

¹¹⁸ K. N. Zelenin and Z. M. Matveeva, *Zh. Org. Khim.* **6**, 717 (1970).

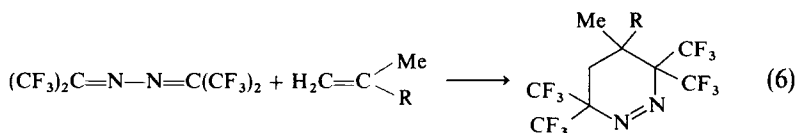
¹¹⁹ K. N. Zelenin, Z. M. Matveeva, and L. Yu. Ermolaeva, *Zh. Org. Khim.* **6**, 723 (1970).

¹²⁰ K. N. Zelenin, V. A. Nikitin, N. M. Anodina, and Z. M. Matveeva, *Zh. Org. Khim.* **8**, 1438 (1972).

the hydrazide and *N*-bromosuccinimide and used immediately, for example, in the reaction with 2,3-dimethylbutadiene as shown in Eq. (5).¹²¹



Hexafluoroacetone azine undergoes cycloaddition reactions with various electron-rich olefins or 1,3-dienes at moderate temperature to give pyridazines [Eq. (6)].¹²² Depending on the structure and the quantity of the olefin employed and the temperature, other mono or bicyclic heterocycles can be formed.



Diazines, triazines, and tetrazines react with electron-rich dienophiles as well as with electron-deficient dienophiles by a (4 + 2)-cycloaddition reaction. The reaction between 1,2,4-triazines and *N,N*-diethylaminopropyne does not give pyridazines as reported previously,¹²³ but the corresponding pyrimidines.¹²⁴

s-Tetrazines have been allowed to react with many alkenes and alkynes to give pyridazines. Monoaryl-1,2,4,5-tetrazines react with phenylacetylene very slowly at room temperature to give mainly the 3,4-diaryl- and a little of the 3,5-diarylpyridazine. From ketene acetals and **24**, either **25** or **26** are formed, depending on the acetal used.¹²⁵ On the other hand, methylacetylene gives only 3-aryl-5-methylpyridazine.¹²⁶ Dipyridyltetrazine and phenylacetylene give 4-phenyl-3,6-(bispyridyl)pyridazines.¹²⁷ Pyridazines are also formed from dimethyl 1,2,4,5-tetrazine-3,6-dicarboxylate and mono- or

¹²¹ J. L. Miesel, *Tetrahedron Lett.*, 3847 (1974).

¹²² S. E. Armstrong and A. E. Tipping, *J. Fluorine Chem.* **3**, 119 (1973).

¹²³ H. Neunhoeffer and H. W. Frühauf, *Tetrahedron Lett.*, 3151 (1969).

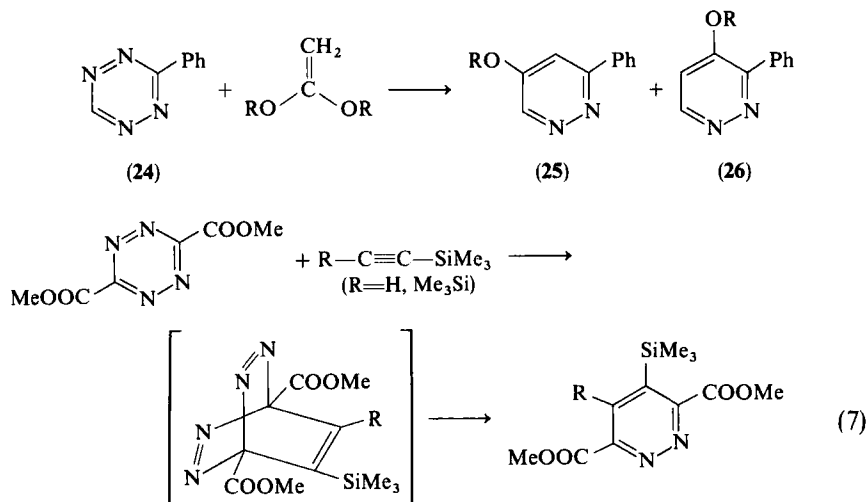
¹²⁴ H. Neunhoeffer and H. W. Frühauf, *Tetrahedron Lett.*, 3355 (1970).

¹²⁵ B. Burg, W. Dittmar, H. Reim, A. Steigel, and J. Sauer, *Tetrahedron Lett.*, 2897 (1975).

¹²⁶ O. Meresz and P. A. Foster-Verner, *Chem. Commun.*, 950 (1972).

¹²⁷ F. H. Case, *J. Heterocycl. Chem.* **5**, 431 (1968).

bis(trimethylsilyl)acetylene as shown in Eq. (7).¹²⁸ The trimethylsilyl group on the pyridazine ring is stable in the presence of acids. Other tetrazines have been used for similar syntheses,¹²⁹ and stannylalkynes give the corresponding pyridazines in which the stannyl group is readily replaced by hydrogen with acetic acid.¹³⁰



The preparation of pyridazines by cycloaddition of ynamines to 1,2,4,5-tetrazines, followed by extrusion of nitrogen, has been described.¹³¹ However, when 1-diethylaminopropyne reacted with 1,2,4,5-tetrazine-3,6-dicarboxamides (**27**; $n = 4, 5$) besides the corresponding pyridazines (**28**), almost equal amounts of the new tetrazines (**29**) were also obtained.¹³² These are formed by addition of the ynamine across the amide carbonyl.

Reaction of 1,4-dihydronaphthalene-1,4-imine with di-pyridyl-1,2,4,5-tetrazine, designed to prepare isoindoles, also gives 3,6-di-pyridyl-pyridazine.¹³³ Other bicyclic alkenes react similarly.¹³⁴⁻¹³⁶ Pyridazines are also formed in reactions between 1,2,4,5-tetrazines and dioxene,

¹²⁸ L. Birkofer and R. Stilke, *J. Organometal. Chem.* **74**, C1 (1974).

¹²⁹ N. J. Hales and H. Heaney, *Tetrahedron Lett.*, 4075 (1975).

¹³⁰ W. P. Neumann and F. G. Kleiner, *Justus Liebigs Ann. Chem.* **716**, 29 (1968).

¹³¹ A. Steigel and J. Sauer, *Tetrahedron Lett.*, 3357 (1970).

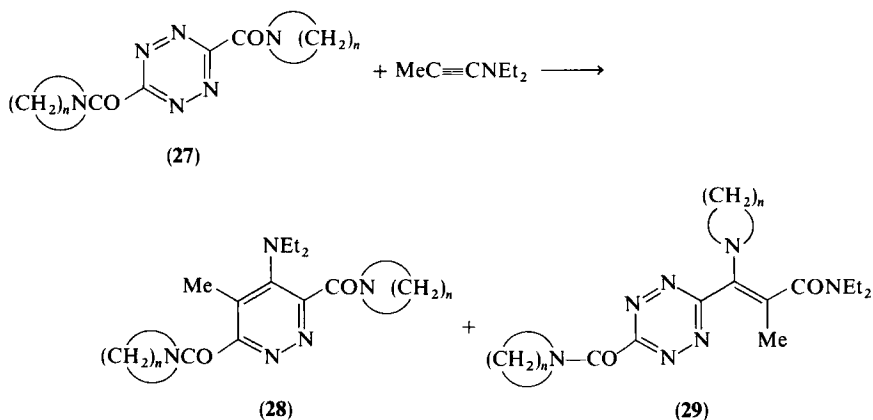
¹³² D. Greatbanks and J. K. Landquist, *Tetrahedron Lett.*, 1659 (1972).

¹³³ G. M. Priestley and R. N. Warrener, *Tetrahedron Lett.*, 4295 (1972).

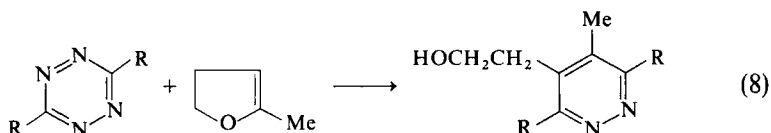
¹³⁴ I. W. McCay and R. N. Warrener, *Tetrahedron Lett.*, 4779 (1970).

¹³⁵ P. L. Watson and R. N. Warrener, *Aust. J. Chem.* **26**, 1725 (1973).

¹³⁶ W. S. Wilson and R. N. Warrener, *Chem. Commun.*, 211 (1972).



ethoxyacetylene, 2,3-dihydropyran, or 5-methyl-2,3-dihydrofuran [Eq. (8)].¹³⁷ Cyclic enol ethers give first the intermediate bicyclic dihydropyridazine adducts that isomerize by ring cleavage to pyridazines with hydroxyalkyl or alkoxyalkyl substituents. Several other alkenes were also used in the reaction with tetrazines to give pyridazines.¹³⁸⁻¹⁴⁰



With heterocyclic dienophiles, however, tetrazines react quite differently: with thiophene and 1-methylimidazole, they form bicyclic products whereas, with 1-methylpyrrole a complex reaction involving a second cycloaddition forms the bispyridazine **30**. The cycloaddition of 2,5-dimethylfuran is followed by ring opening to give **31**¹⁴¹ and with methylenethietane a spiro-pyridazine derivative **32** is formed¹⁴² (Scheme 1).

Cycloaddition of 1,2,4-triazoline-3,5-dione or its 4-phenyl analog to penta-2,4-dienoic acid first affords the cycloadduct **33**. This, upon hydrogenation to **34** and alkaline hydrolysis, gives hexahydropyridazine-3-carboxylic acid (piperazic acid) (**35**),¹⁴³ a constituent of the monamycine cyclohexadepsipeptides.

¹³⁷ P. Roffey and J. P. Verge, *J. Heterocycl. Chem.* **6**, 497 (1969).

¹³⁸ J. A. Deyrup and H. L. Gingrich, *Tetrahedron Lett.*, 3115 (1977).

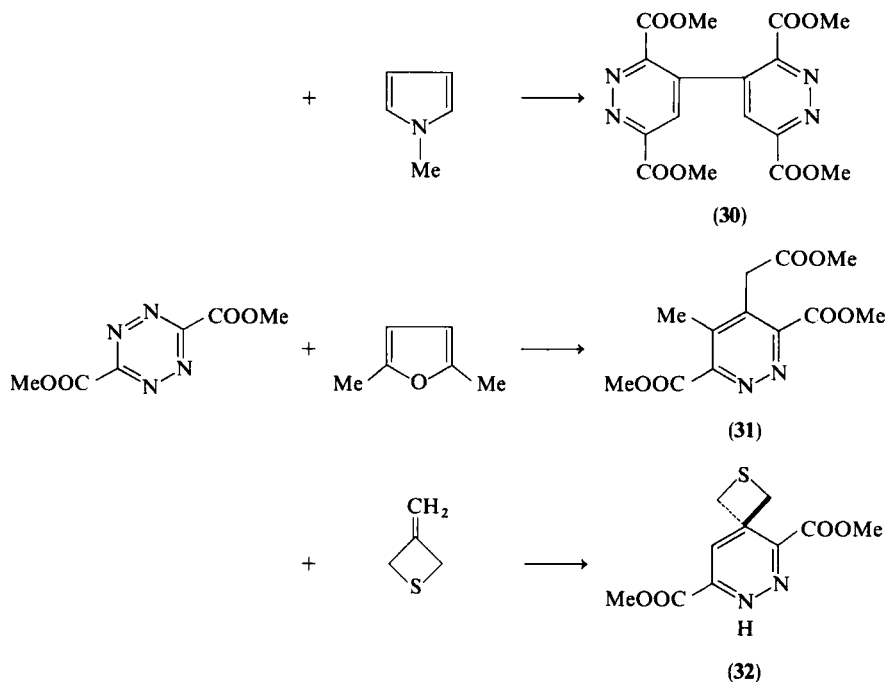
¹³⁹ H. Neunhoeffer and M. Bachmann, *Chem. Ber.* **108**, 3877 (1975).

¹⁴⁰ W. Skorianetz and E. Kovats, *Helv. Chim. Acta* **54**, 1922 (1971).

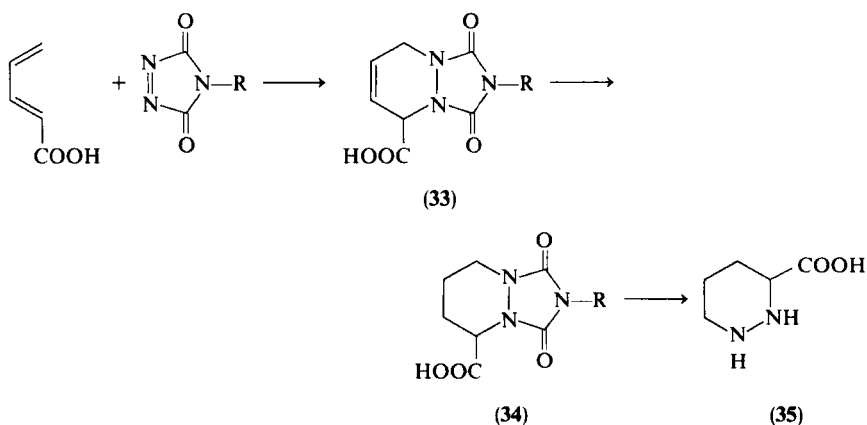
¹⁴¹ G. Seitz and T. Kämpchen, *Chem.-Ztg.* **99**, 292 (1975).

¹⁴² G. Seitz and T. Kämpchen, *Arch. Pharm. (Weinheim)* **308**, 237 (1975).

¹⁴³ C. R. Davies and J. S. Davies, *J.C.S. Perkin I*, 2390 (1976).



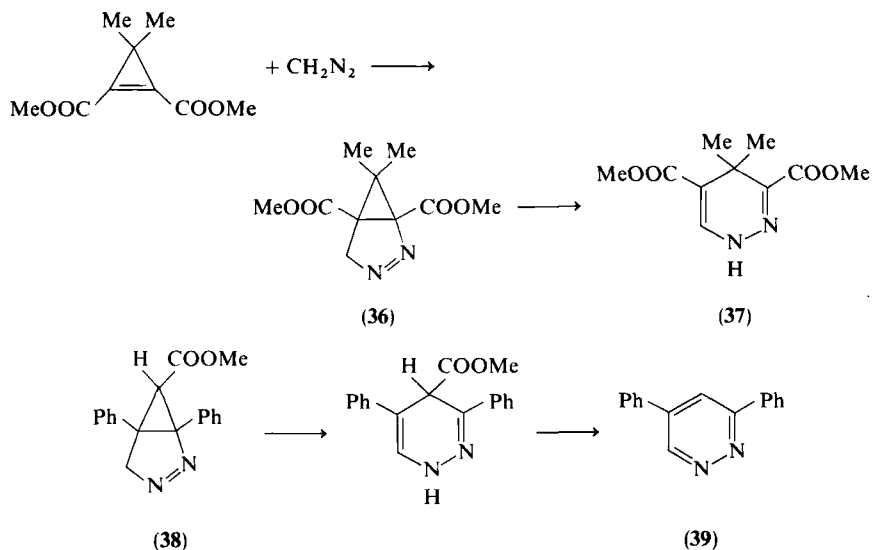
SCHEME 1



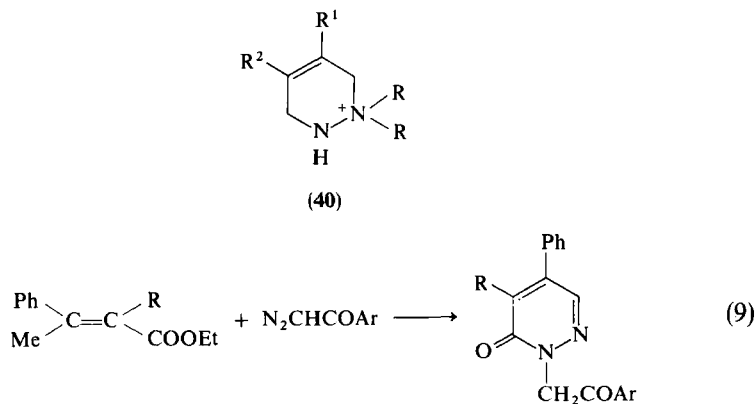
Cycloadditions are known with diazoalkanes and related compounds. Diazomethane reacts with a cyclopropene and the pyrazoline cycloadduct (36) is rearranged by acid to the pyridazine 37.¹⁴⁴ Similarly, the cycloadduct

¹⁴⁴ M. Franck-Neumann and C. Buchecker, *Tetrahedron Lett.*, 2659 (1969).

38 is converted by alkali or acid into 3,5-diphenylpyridazine (**39**).^{145,146} Reactions with other diazocompounds proceed similarly.¹⁴⁷



Other pyridazine syntheses include reactions between methyl 1,2-dimethylcyclopropenecarboxylate and methyl diazoacetate,¹⁴⁸ and between



¹⁴⁵ M. I. Komendantov and R. R. Bektukhametov, *Zh. Org. Khim.* 7, 423 (1971).

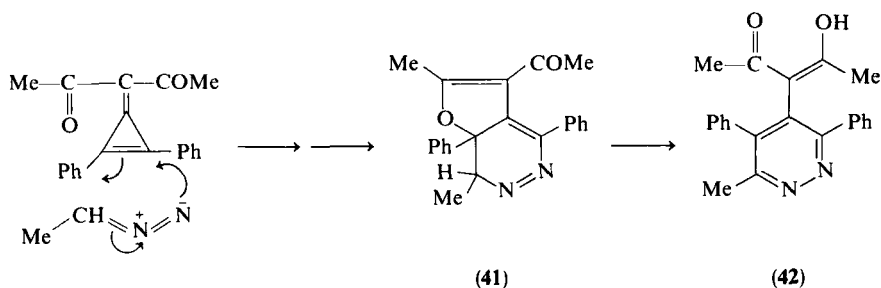
¹⁴⁶ M. I. Komendantov, R. R. Bektukhametov, and V. G. Novinskii, *Zh. Org. Khim.* 12, 801 (1976).

¹⁴⁷ L. G. Zaitseva, I. B. Avezov, O. A. Subbotin, and I. G. Bolesov, *Zh. Org. Khim.* 11, 1415 (1975).

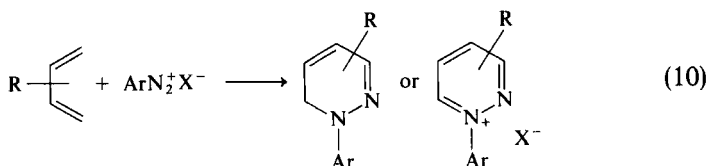
¹⁴⁸ H. Prinzbach and H. D. Martin, *Chimia* 23, 37 (1969).

bis(diisopropylamino)cyclopropenium perchlorate and excess of a diazoalkane.¹⁴⁹ Diazenium cations, formed from either 1,1-dimethyl- or 1,1-dibenzylhydrazine, readily form cycloadducts with dienes to give tetrahydropyridazinium salts **40**.^{150–152} In another example, diazomethylketones are converted by methyl-substituted cinnamic esters into pyridazines [Eq. (9)].¹⁵³

The addition of diazoalkanes to methylene cyclopropenes gives pyridazines. A labile 1:1 adduct (**41**) was isolated in the case of diazoethane, thus indicating the reaction sequence leading to **42** as the product.¹⁵⁴



Pyridazinium salts or 1,6-dihydropyridazines have been obtained in cycloaddition reactions between aromatic and heterocyclic diazo compounds and dienes [Eq. (10)].¹⁵⁵ Diazoheterocycles usually cycloadd as 1,3-dipoles.



There are, however, a few exceptions since they can react also as 1,2-dipoles. For example, 3-diazopyrazolo-[3,4-b]pyridine reacts with 2,3-dimethylbutadiene to give the pyridazinium salt **43**,¹⁵⁶ and in a similar manner diazocyanoimidazole and butadiene gave a dihydropyridazine derivative.¹⁵⁷

¹⁴⁹ Z. Yoshida, H. Konishi, K. Hayashi, and H. Ogoshi, *Heterocycles* **5**, 401 (1976).

¹⁵⁰ G. Cauquis, B. Chabaud, and M. Genies, *Tetrahedron Lett.*, 2389 (1974).

¹⁵¹ K. N. Zelenin and I. P. Bezhan, *Khim. Geterotsikl. Soedin.*, 93 (1970).

¹⁵² K. N. Zelenin and I. P. Bezhan, *Zh. Org. Khim.* **6**, 2206 (1970).

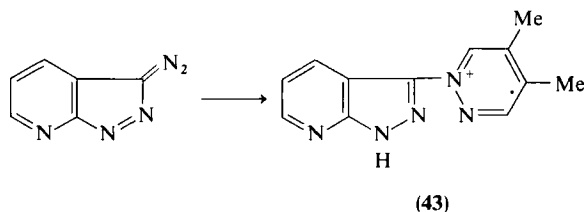
¹⁵³ E. Fanghänel, K. Gewald, K. Pütsch, and K. Wagner, *J. Prakt. Chem.* **311**, 388 (1969).

¹⁵⁴ T. Eicher and E. Angerer, *Chem. Ber.* **103**, 339 (1970).

¹⁵⁵ B. A. Carlson, W. A. Sheppard, and O. W. Webster, *J. Am. Chem. Soc.* **97**, 5291 (1975).

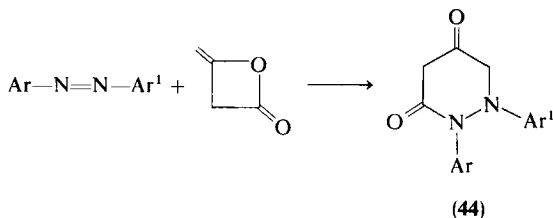
¹⁵⁶ M. Kočevár, B. Stanovnik, and M. Tišler, *Heterocycles* **6**, 681 (1977).

¹⁵⁷ W. A. Sheppard and O. W. Webster, *J. Am. Chem. Soc.* **95**, 2695 (1973).



In other examples of the use of azo compounds in pyridazine synthesis, dialkyl azodicarboxylates undergo cycloaddition with dienes to give 1,2,3,6-tetrahydropyridazines.¹⁵⁸⁻¹⁶³ Azobis(formamidine) reacts similarly.¹⁶⁴

Diethyl azodicarboxylate also reacts with furans to give an adduct which is transformed into a pyridazine by acid.¹⁶⁵ In a photochemical synthesis, 1,2-diarylhexasahydropyridazine-3,5-diones (**44**) are formed from azobenzenes and diketene.¹⁶⁶



C. FROM OTHER HETEROCYCLES

A variety of heterocycles are suitable for pyridazine syntheses. Among other products, pyridazines (**45**) are obtained from titanium tetrachloride-induced cleavage of arylazirines at -78°C .¹⁶⁷ Similarly, the spiro-pyridazinone **46** is obtained from a diaziridine and diphenylcyclopropanone.¹⁶⁸

¹⁵⁸ M. Fetizon, M. Golfier, R. Milcent, and I. Papadakis, *Tetrahedron* **31**, 165 (1975).

¹⁵⁹ J. Firl, *Chem. Ber.* **102**, 2169 (1969).

¹⁶⁰ S. K. Karagezyan and G. T. Tatevosyan, *Arm. Khim. Zh.* **21**, 179 (1968) [*CA* **69**, 96626 (1968)].

¹⁶¹ E. Koerner von Gustorf, *Tetrahedron Lett.*, 4693 (1968).

¹⁶² M. J. Kornet and H. S. I. Tan, *J. Pharm. Sci.* **61**, 1936 (1972).

¹⁶³ T. Sasaki, S. Eguchi, and T. Ishii, *J. Org. Chem.* **34**, 3749 (1969).

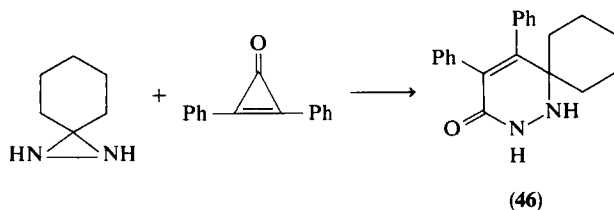
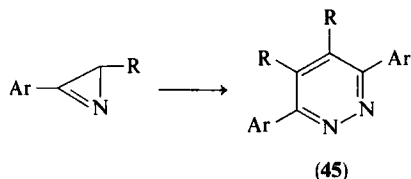
¹⁶⁴ G. Pirisino and F. Sparatore, *Boll. Chim. Farm.* **113**, 421 (1974).

¹⁶⁵ K. N. Zelenin and I. P. Bezhan, *Khim. Geterotsikl. Soedin., Sb. 2: Kislorodsoderzhashchie Geterotsikly*, 129 (1970) [*CA* **76**, 140695 (1972)].

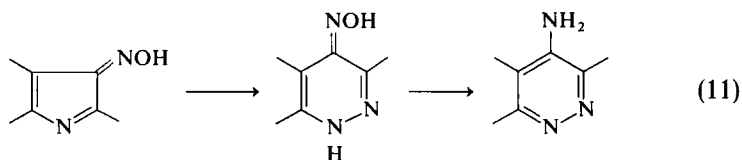
¹⁶⁶ T. Kato, M. Sato, and K. Tabei, *J. Org. Chem.* **39**, 3205 (1974).

¹⁶⁷ H. Alper, J. E. Prickett, and S. Wollowitz, *J. Am. Chem. Soc.* **99**, 4330 (1977).

¹⁶⁸ J. W. Lown, *J. Chem. Soc. C*, 1338 (1969).



4-Aminopyridazines are conveniently obtained from isonitroso pyrroles as shown in Eq. (11). The reduction can be accomplished either with aluminum in the presence of alkali or, preferably, with hydrazine.¹⁶⁹ 2,5-Diiminopyrrolidine (succinimidine) or succinonitrile gives with hydrazine 3,6-dihydrazino-4,5-dihydropyridazine.^{170,171}



Furans continue to be useful synthons for pyridazine syntheses. A detailed investigation of the reaction between ethyl 2-methoxy-2-methyl-3-oxofuran-4-carboxylate (**47**) and hydrazines revealed that, depending upon reaction conditions, compound **49**, a mixture of **48** and **49** or, in addition to these, also **50**, is obtained.^{172,173} Similarly, ethyl 5-nitrofuran-3-carboxylate and hydrazine yield a pyridazine, probably by addition, ring opening of the furan, and recyclization [Eq. (12)].¹⁷⁴ Another synthesis involves electrolytic methoxylation of a furan derivative and subsequent treatment with hydrazine.¹⁷⁵

¹⁶⁹ T. Aiello, S. Giambrone, and L. Giammanco, *Atti Accad. Sci., Lett. Arti Palermo, Parte I* **30**, 77 (1969–1970).

¹⁷⁰ J. A. Elvidge and J. A. Pickett, *J.C.S. Perkin I*, 2346 (1972).

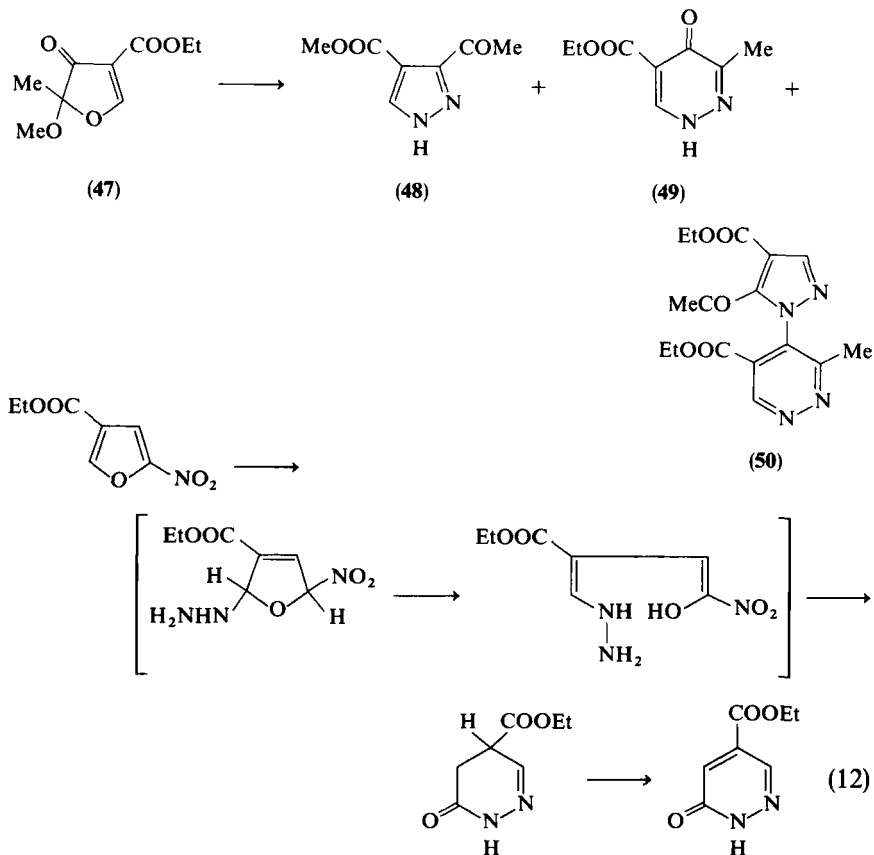
¹⁷¹ I. M. Shanazarova and P. A. Volkova, *Khim. Geterotsikl. Soedin.*, 1420 (1974).

¹⁷² P. Battesti, O. Battesti, and M. Selim, *Bull. Soc. Chim. Fr.*, 2185 (1975).

¹⁷³ S. Gelin and R. Gelin, *J. Heterocycl. Chem.* **14**, 75 (1977).

¹⁷⁴ B. Jägersten, *Ark. Kemi* **30**, 261 (1969).

¹⁷⁵ K. Yu. Novitskii and E. F. Kasyanova, *Khim. Geterotsikl. Soedin.*, 1306 (1970).



Several transformations of pyrazoles into pyridazines have been reported. In a carbene ring expansion, 3,4,5-trimethylpyrazole was treated with dichlorocarbene under neutral conditions. A very small amount of a pyridazine (51) together with a pyrimidine and two pyrazole derivatives were obtained.¹⁷⁶ Under basic conditions no pyridazine was formed and the major product was the pyrazole 52, which could be rearranged with sodium ethoxide at 125° into the pyridazine 53.¹⁷⁷ Pyridazines are formed also from certain pyrazoles upon heating, for example 54,^{178,179} or from some pyrazolines.^{180,181}

¹⁷⁶ R. L. Jones and C. W. Rees, *J. Chem. Soc. C*, 2251 (1969).

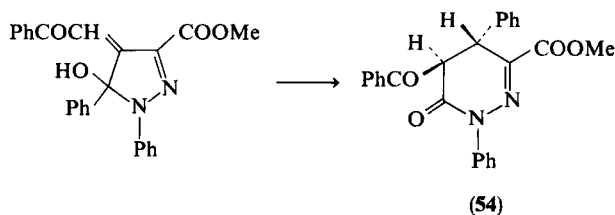
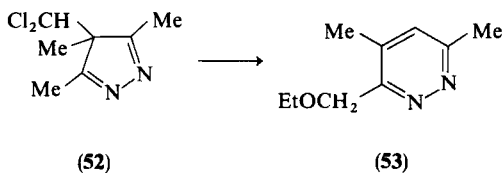
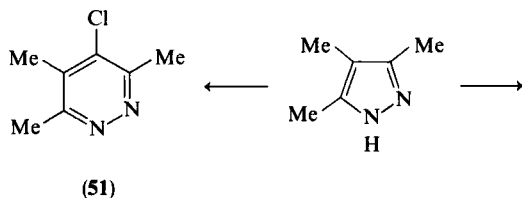
¹⁷⁷ R. L. Jones and C. W. Rees, *J. Chem. Soc. C*, 2255 (1969).

¹⁷⁸ R. Fusco and P. Dalla Croce, *Tetrahedron Lett.*, 4591 (1970).

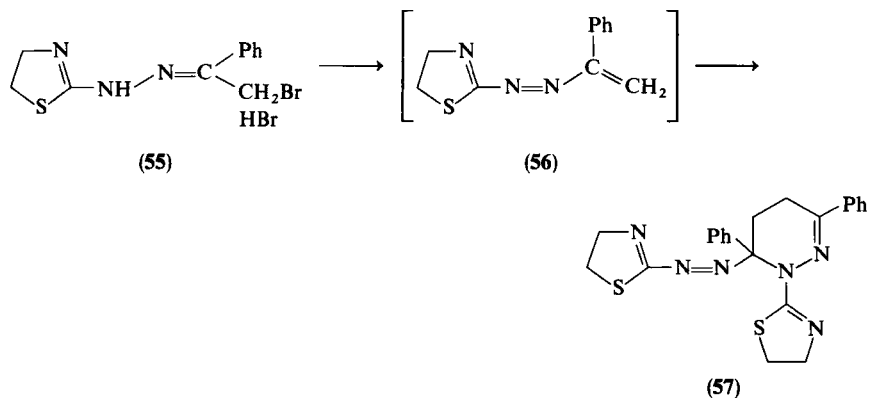
¹⁷⁹ R. Fusco and P. Dalla Croce, *Gazz. Chim. Ital.* **102**, 431 (1972).

¹⁸⁰ M. Lempert-Sreter and K. Lempert, *Tetrahedron* **31**, 1677 (1975).

¹⁸¹ G. Westphal and H. H. Stroh, *Justus Liebigs Ann. Chem.* **716**, 160 (1968).



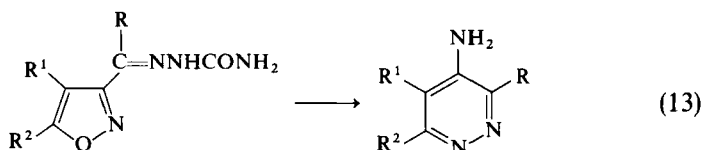
In an attempt to prepare a bicyclic compound from the thiazoline **55** and a base, a pyridazine (**57**) was obtained in moderate yield. It is postulated that the unisolated intermediate **56** undergoes a (4 + 2)-cycloaddition to give the final product.¹⁸²



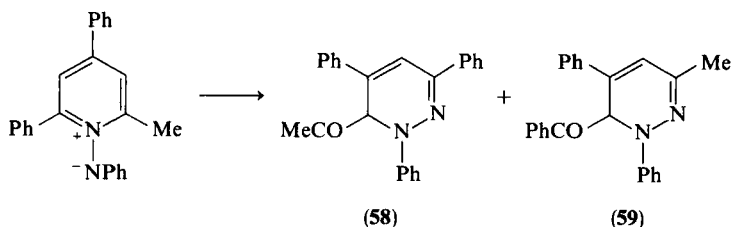
Properly substituted isoxazoles are also a potential source of pyridazines. For example, hydrogenation (Raney Ni) of semicarbazones of 3-acyl-

¹⁸² K. H. Ongania and J. Schantl, *Monatsh. Chem.* **107**, 481 (1976).

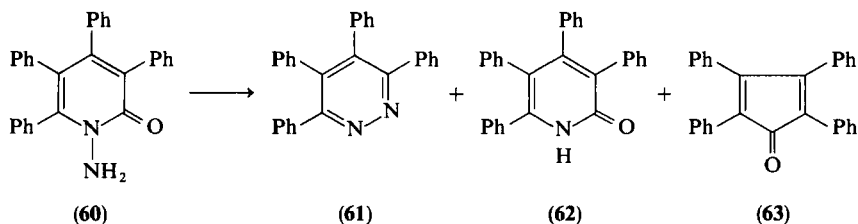
isoxazoles affords 4-aminopyridazines as shown in Eq. (13).¹⁸³ Similarly, hydrogenation of phenylhydrazones gives first open-chain products; upon treatment with alkali, pyridazin-4-ones are obtained.¹⁸⁴



1,6-Dihydropyridazines were prepared for the first time by a peroxide-induced rearrangement of 1-phenyliminopyridines. The isomers **58** and **59** originate from peroxide attack either at C-2 or C-5 of the pyridine ring, followed by ring opening and recyclization.¹⁸⁵



A new type of rearrangement is described by Rees and Yelland^{186,187}; the 1-aminopyridone **60** when oxidized with lead tetraacetate gives the pyridazine **61** as the main product and a small amount of **62** and **63**. It is supposed that the reaction proceeds via a nitrene, followed by ring expansion, valence isomerization, and extrusion of carbon monoxide.



There are several examples of pyridazine formation from seven-membered precursors, in particular diazepines. 2-Tosyldiazepin-4-one rearranges in the presence of sodium alkoxide or cyanide ion in methanol to a pyridazine. The

¹⁸³ V. Sprio and E. Ajello, *Ann. Chim. (Rome)* **57**, 846 (1967).

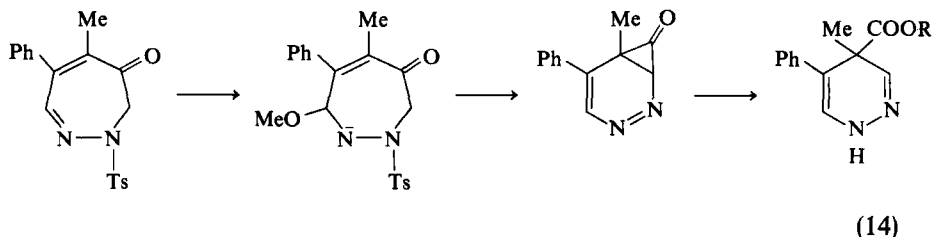
¹⁸⁴ V. Sprio and E. Ajello, *Ann. Chim. (Rome)* **58**, 128 (1968).

¹⁸⁵ V. Snieckus and G. Kan, *Tetrahedron Lett.*, 2267 (1970).

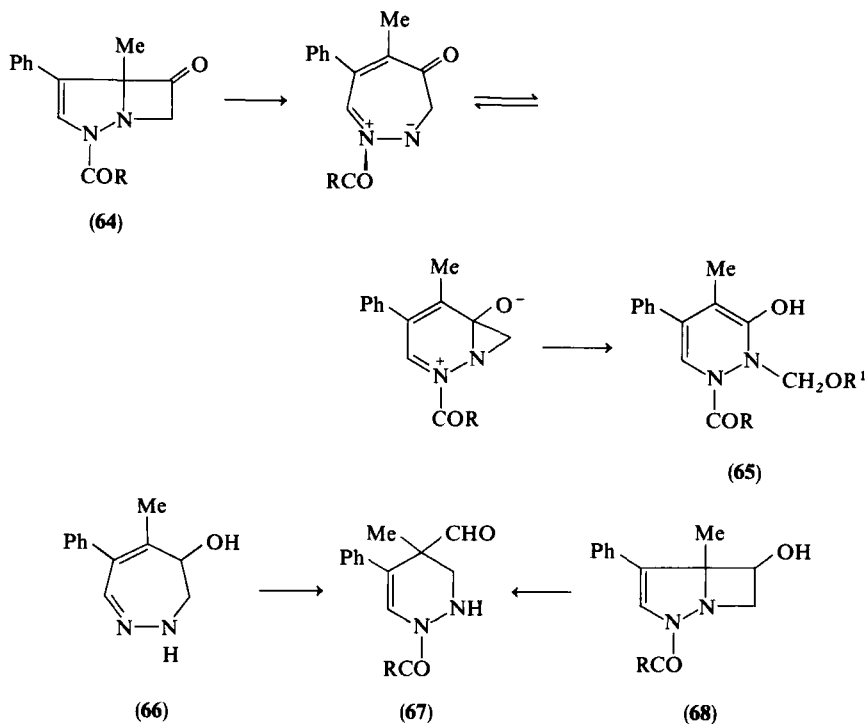
¹⁸⁶ C. W. Rees and M. Yelland, *J.C.S. Perkin I*, 77 (1972).

¹⁸⁷ C. W. Rees and M. Yelland, *Chem. Commun.*, 377 (1969).

reaction involves addition of alkoxide, with elimination of toluenesulfonic acid, and a bicyclic ketone is postulated as intermediate [Eq. (14)].¹⁸⁸ A



diazepine and its bicyclic valence isomer are proposed as intermediates in the conversion of bicyclic ketones **64** into pyridazines **65**, with other products.¹⁸⁹ Acylation of the diazepinol **66** gives the pyridazine **67**, formed also in a thermal rearrangement from the bicyclic alcohols **68**.¹⁹⁰ The latter are not intermediates in the conversion of **66** into **67**. However, the ketone **69**,

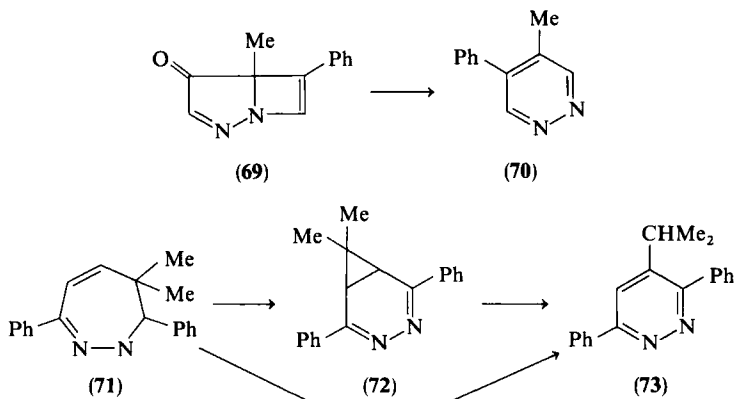


¹⁸⁸ J. A. Moore, E. J. Volker, and C. M. Kopay, *J. Org. Chem.* **36**, 2676 (1971).

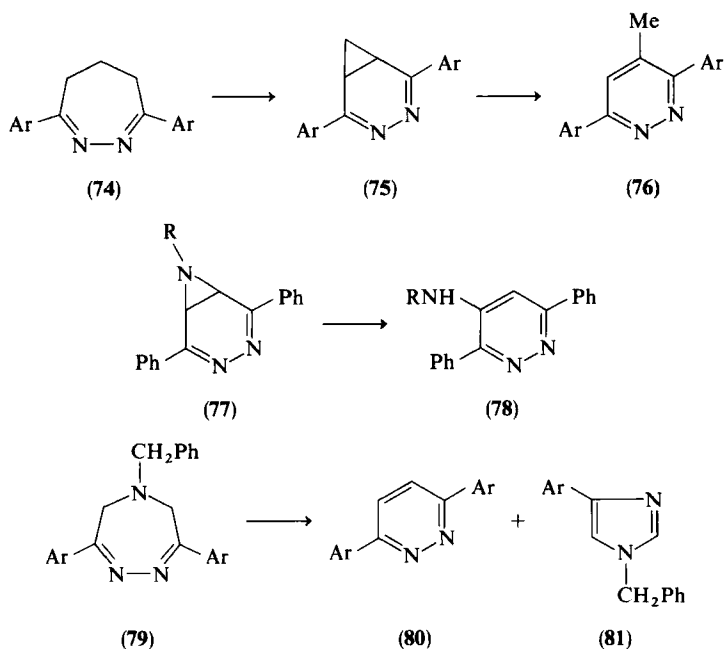
¹⁸⁹ J. A. Moore, B. Staskun, and J. F. Blount, *J. Org. Chem.* **41**, 3156 (1976).

¹⁹⁰ S. M. Rosen and J. A. Moore, *J. Org. Chem.* **37**, 3770 (1972).

upon thermolysis at 475°C, is transformed into the pyridazine **70** in moderate yield¹⁹¹: valence isomerization via a diazotropone is postulated. The



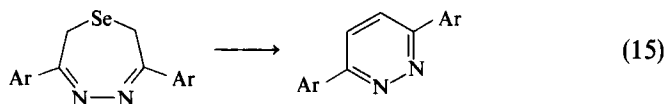
diazepine **71** is thermally converted into the diazanorcaradiene (**72**), which with acid gives the pyridazine **73**, formed in a similar manner also from the diazepine **71**.¹⁹² On the other hand, 1,2-diazepines **74** upon halogenation



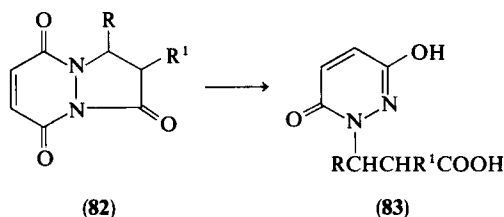
¹⁹¹ E. J. Völcker, M. G. Pleiss, and J. A. Moore, *J. Org. Chem.* **35**, 3615 (1970).

¹⁹² H. E. Zimmermann and W. Eberbach, *J. Am. Chem. Soc.* **95**, 3970 (1973).

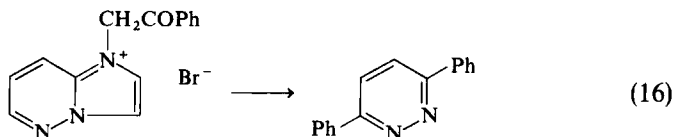
give pyridazines **76** via the norcaradiene **75**.^{193,194} The azanorcaradiene **77** gives upon photolysis a 1,2,4-triazepine as the major product, accompanied by 6% of the pyridazine **78**,¹⁹⁵ considered to arise from the triplet state. The triazepine **79** gives on bromination the pyridazine **80** or the imidazole **81** as the main product, depending upon the reaction conditions.¹⁹⁶ 3,6-Diarylpyridazines can be obtained also from 1,4,5-selenadiazepines upon heating in ethylene glycol (Eq. 15).¹⁹⁷



There are examples of pyridazine formation from bicyclic heterocycles. 1-Substituted carboxyalkylpyridazines (**83**) are obtained by alkaline hydrolysis of the corresponding pyrazolo[1,2-*a*]pyridazines (**82**), obtainable from maleic hydrazide and chlorides of α,β -unsaturated acids.¹⁹⁸ 1-Phenacyl-



limidazo[1,2-*b*]pyridazinium bromides, when treated with hydrazine, are transformed into 3,6-diphenylpyridazine (Eq. 16).¹⁹⁹ Evidently, the carbon



skeleton of the pyridazine originates from the phenacyl group, the original heterocycle simply playing the role of a leaving group.

¹⁹³ R. G. Amiet and R. B. Johns, *Aust. J. Chem.* **21**, 1279 (1968).

¹⁹⁴ O. Tsuge and K. Kamata, *Heterocycles* **3**, 15 (1975).

¹⁹⁵ I. Saito, A. Yazaki, and T. Matsuura, *Tetrahedron Lett.*, 2459 (1976).

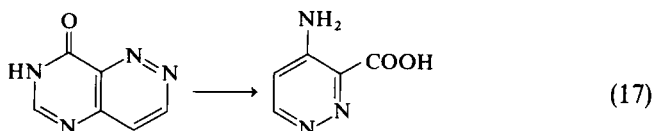
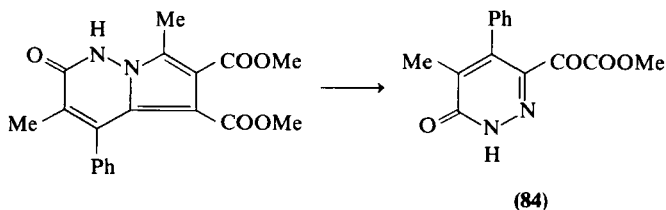
¹⁹⁶ O. Tsuge and K. Kamata, *Heterocycles* **3**, 547 (1975).

¹⁹⁷ E. Ajello, *J. Heterocycl. Chem.* **9**, 1427 (1972).

¹⁹⁸ M. Dormoy, J. Godin, and A. Le Berre, *Bull. Soc. Chim. Fr.*, 4222 (1968).

¹⁹⁹ B. Koren, B. Stanovnik, and M. Tišler, *J. Heterocycl. Chem.* **11**, 471 (1974).

Permanganate oxidation of a pyrrolo[1,2-*b*]pyridazine gives the pyridazine **84**²⁰⁰ and 4-aminopyridazine-5-carboxylic or -4,5-dicarboxylic acid are obtained by oxidation of pyridopyridazines.²⁰¹ Aminopyridazinecarboxylic acids are also obtainable by hydrogenolysis of *s*-triazolo[4,3-*b*]pyridazines^{202,203} or upon treatment of pyrimido[4,5-*c*]-, pyrimido[5,4-*c*]- or pyrimido[4,5-*d*]pyridazines with hot alkali or ammonia (Eq. 17).^{204–206}



3,6-Dimethylpyridazine-4,5-dicarboxylic acid is obtained by permanganate oxidation of the corresponding pyridazino[4,5-*d*]- or furo[3,4-*d*]pyridazine.²⁰⁷ A good yield of 3-chloro-4,5-diaminopyridazin-6(1*H*)-one is obtained from [1,2,5]thiadiazolo[3,4-*d*]pyridazine and alkali as shown in Eq. (18),²⁰⁸ the 4-hydroxy analog reacted similarly.²⁰⁹ During the preparation of pyrazino[2,3-*d*]pyridazinedione (**85**) under certain conditions the pyridazine **86** is formed as by-product. It is supposed that **85** is reduced by diimide, with subsequent ring opening of the pyrazine ring.²¹⁰

5-Dialkylaminopyridazine-1-oxides (**87**) have been prepared by condensation of 1,3,4-oxadiazine-6-one 4-oxides with ynamines.²¹¹ The synthesis is regiospecific, and upon deoxygenation the corresponding 4-dialkylaminopyridazines are obtained.

²⁰⁰ J. A. Moore, R. C. Geahart, O. S. Rothenberger, P. C. Thorstenson, and R. H. Wood, *J. Org. Chem.* **37**, 3774 (1972).

²⁰¹ D. B. Paul and H. J. Rodda, *Aust. J. Chem.* **22**, 1745 (1969).

²⁰² H. G. O. Becker and H. Böttcher, *Tetrahedron* **24**, 2687 (1968).

²⁰³ H. G. O. Becker, H. Böttcher, R. Erbsch, and G. Schmoz, *J. Prakt. Chem.* **312**, 780 (1970).

²⁰⁴ T. Kinoshita and R. N. Castle, *J. Heterocycl. Chem.* **5**, 845 (1968).

²⁰⁵ T. Nakagome, R. N. Castle, and H. Murakami, *J. Heterocycl. Chem.* **5**, 523 (1968).

²⁰⁶ M. Yanai, T. Kinoshita, H. Watanabe, and S. Iwasaki, *Chem. Pharm. Bull.* **19**, 1849 (1971).

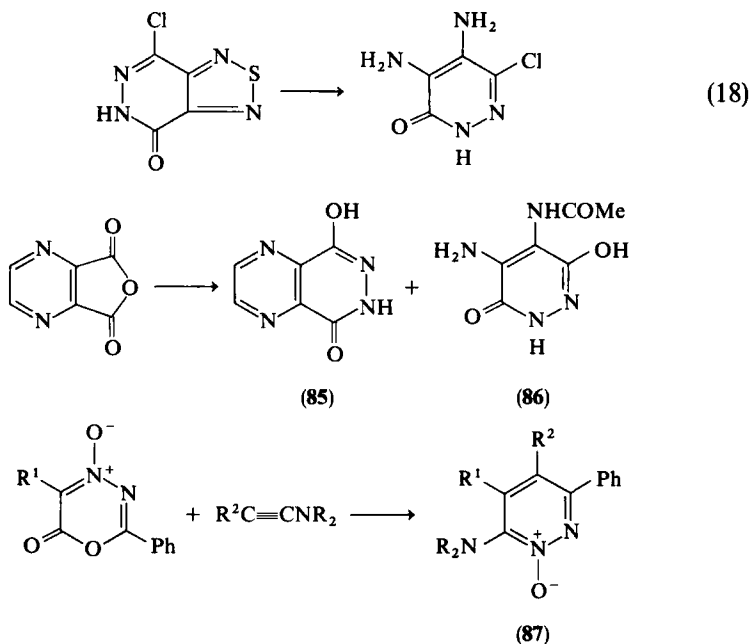
²⁰⁷ G. Adembri and M. Scotton, *J. Chem. Soc. C*, 1536 (1970).

²⁰⁸ D. Pichler and R. N. Castle, *J. Heterocycl. Chem.* **8**, 441 (1971).

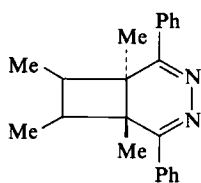
²⁰⁹ I. Sekikawa, *J. Heterocycl. Chem.* **6**, 129 (1969).

²¹⁰ D. B. Paul, *Aust. J. Chem.* **27**, 1331 (1974).

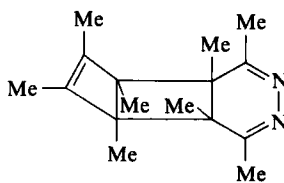
²¹¹ J. P. Freeman and R. C. Grabiak, *J. Org. Chem.* **41**, 3970 (1976).



In a study of valence isomerizations of the diazabicyclooctadiene-diazacyclooctatriene system, it was found that the bicyclic compound **88** at 180° generated 4,5-dimethyl-3,6-diphenylpyridazine.²¹² Similarly, irradiation of the tricyclic structure **89** afforded quantitatively 3,4,5,6-tetramethylpyridazine and the cyclobutadiene dimer.²¹³ The bicyclic



(88)



(89)

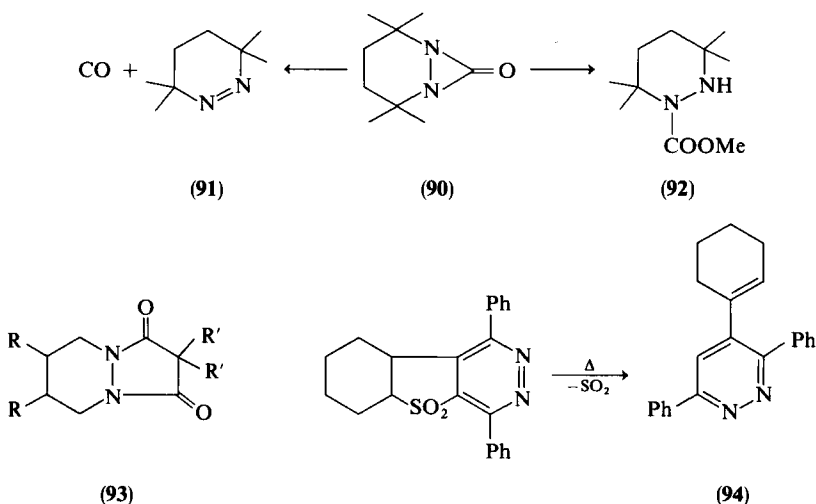
diaziridinone **90** is decarbonylated at room temperature to **91**; in methanol the product is **92**.²¹⁴ Piperidazines (hexahydropyridazines) are formed on alkaline hydrolysis of hexahydropyrazolo[1,2-*a*]pyridazine-1,3-diones

²¹² G. Maier, U. Heep, M. Wiessler, and M. Strasser, *Chem. Ber.* **102**, 1928 (1969).

²¹³ G. Maier, and M. Schneider, *Angew. Chem.* **83**, 885 (1971).

²¹⁴ C. A. Renner and F. D. Greene, *J. Org. Chem.* **41**, 2813 (1976).

(93),²¹⁵ and also in an improved synthesis from 1,2-diacetylhydrazine.²¹⁶ Thermal decomposition of a benzothieno[2,3-*d*]pyridazine gives in moderate yield the pyridazine 94.²¹⁷



D. FROM CARBOHYDRATES

Recently, several syntheses of pyridazines from monosaccharides have been described. Calcium 2,5-diketo-D-gluconate reacts with monosubstituted hydrazines to give the corresponding pyridazinium derivatives of the zwitterionic type 95.²¹⁸⁻²²⁰ The reaction proceeds by hydrazone formation, dehydration, decarboxylation, and cyclization. In a similar manner, other 2,5-dicarbonyl sugars, like 5-keto-D-fructose, are transformed into 4(1*H*)-pyridazinones.²¹⁹ These are also obtained from D-xylohexos-4-uloses (96) as a mixture of 3- and 6-substituted products (97, 98).²²¹ 4-Hydrazino-4,5-dideoxy-L-xylose is cyclized to a tetrahydropyridazine.²²²

²¹⁵ H. Stetter and P. Woernle, *Justus Liebigs Ann. Chem.* **724**, 150 (1969).

²¹⁶ S. Groszkowski, J. Wrona, and W. Szuflet, *Rocz. Chem.* **47**, 1551 (1973).

²¹⁷ O. Tsuge, S. Iwanami, and S. Hagio, *Bull. Chem. Soc. Jpn.* **45**, 237 (1972).

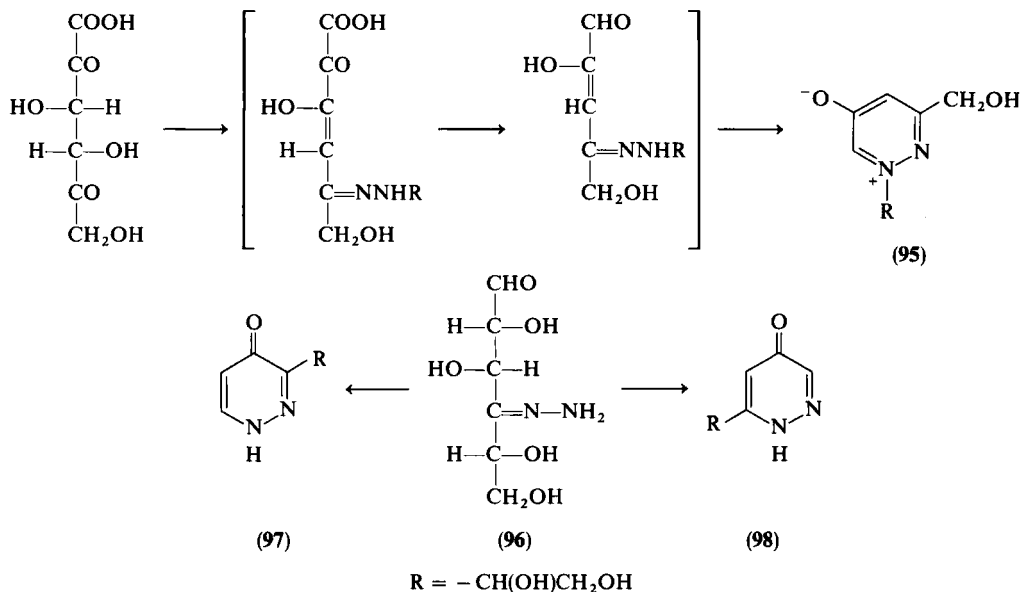
²¹⁸ K. Imada, *Chem. Commun.*, 796 (1973).

²¹⁹ K. Imada and K. Asano, *Chem. Pharm. Bull.* **22**, 1691 (1974).

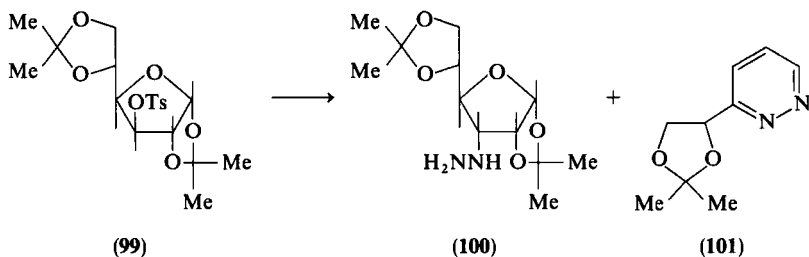
²²⁰ K. Imada, *Chem. Pharm. Bull.* **22**, 1732 (1974).

²²¹ H. Paulsen, K. Steinert, and G. Steinert, *Chem. Ber.* **103**, 1846 (1970).

²²² H. Paulsen and G. Steinert, *Chem. Ber.* **103**, 1834 (1970).



D-Glucufuranose with protected functional groups (**99**), when heated with hydrazine, gives a mixture of the hydrazinopyranose **100** and the pyridazine **101**, which is transformed upon hydrolysis and oxidation into pyridazine-3-carboxylic acid.²²³ The mechanism was studied with labeled starting material.²²⁴



E. PYRIDAZINE 1,2-DIOXIDES

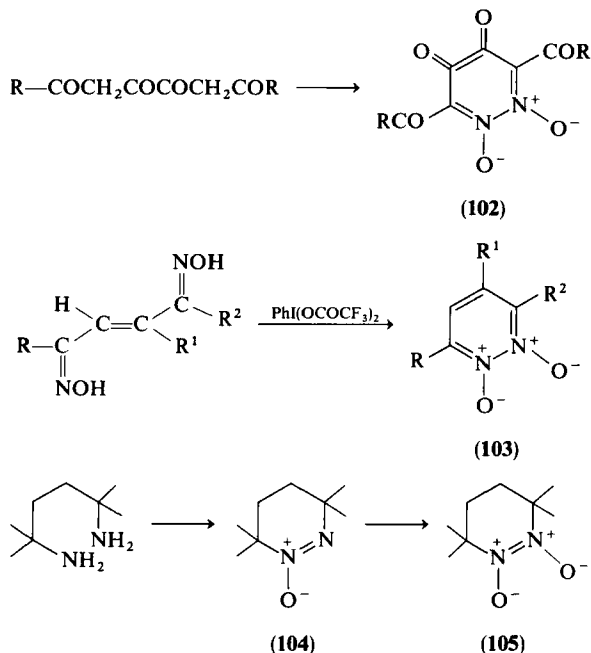
Pyridazine 1,2-dioxides were first obtained in 1968 in poor yield by direct N-oxidation.²²⁵ (for other references see Section III.A). Recently, they have

²²³ P. Smit, G. A. Stork, and H. C. Van der Plas, *J. Heterocycl. Chem.* **12**, 75 (1975).

²²⁴ P. Smit, G. A. Stork, and H. C. Van der Plas, *J. Heterocycl. Chem.* **12**, 957 (1975).

²²⁵ I. Suzuki, M. Nakadate, and S. Sueyoshi, *Tetrahedron Lett.*, 1855 (1968).

been formed from acyclic precursors. The dioxides **102** were obtained from tetraketones and dinitrogen tetroxide.²²⁶ They explode when dry. In another synthesis, dioximes of unsaturated *trans*-1,4-diketones are dehydrogenated with phenyliodine bistrifluoroacetate to give di- and trisubstituted pyridazine 1,2-dioxides (**103**) in moderate yield.²²⁷ When 2,5-diamino-2,5-dimethylhexane is oxidized with hydrogen peroxide in the presence of Na₂WO₄, the cyclic *N*-oxide **104** is obtained. This is transformed into the 1,2-dioxide **105** by *m*-chloroperbenzoic acid.²²⁸



F. PYRIDAZINE GLYCOSIDES

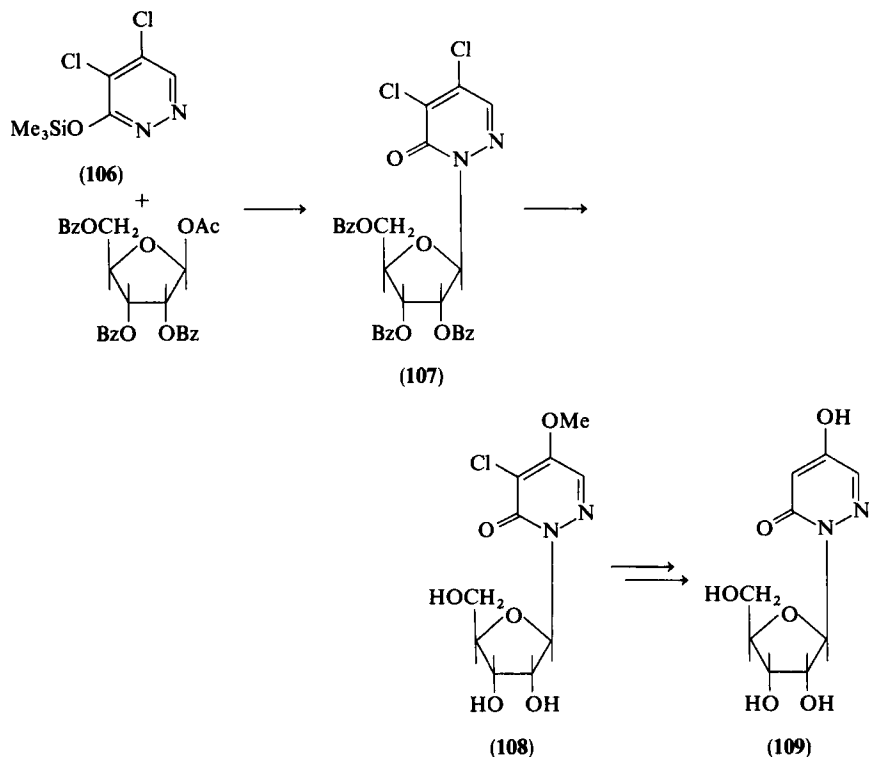
The pyridazine nucleosides, related to the naturally occurring nucleosides cytidine and uridine, have been prepared from 4,5-dichloropyridazin-6-one. Its trimethylsilyl derivative (**106**), when condensed with the protected β -D-ribofuranose, affords the β -nucleoside **107**. From this the cytidine analog is obtained after treatment with ammonia and deprotection or, via the methoxy

²²⁶ B. Unterhalt and U. Pindur, *Arch. Pharm. (Weinheim)* **310**, 264 (1977).

²²⁷ S. Spyroudis and A. Varvoglis, *Synthesis*, 839 (1976).

²²⁸ J. P. Snyder, M. L. Heyman, and E. N. Suci, *J. Org. Chem.* **40**, 1395 (1975).

derivative **108** and after dehalogenation, the uridine analog **109** is prepared (Scheme 2).²²⁹



SCHEME 2

Many new anomeric pyridazine *O*- and *N*-glycosides^{230–242} or *S*- and *N*-glycosides were prepared,^{243–246} and their *O* → *N*-transglycosidation^{230–234,237–242,247} or *S* → *N*-transglycosidation was studied.^{245,248,249}

²²⁹ D. J. Katz, D. S. Wise, and L. B. Townsend, *J. Heterocycl. Chem.* **12**, 609 (1975).

²³⁰ D. Heller and G. Wagner, *Z. Chem.* **10**, 67 (1970).

²³¹ D. Heller and G. Wagner, *Z. Chem.* **10**, 339 (1970).

²³² D. Heller and G. Wagner, *Pharmazie* **27**, 427 (1972).

²³³ D. Heller and G. Wagner, *Pharmazie* **28**, 103 (1973).

²³⁴ H. Pischel and G. Wagner, *Pharmazie* **25**, 45 (1970).

²³⁵ H. Pischel, P. Nuhn, E. Liedmann, and G. Wagner, *J. Prakt. Chem.* **316**, 615 (1974).

²³⁶ G. L. Szekeres, R. K. Robins, and R. A. Long, *J. Carbohydr., Nucleosides, Nucleotides* **1**, 97 (1974).

²³⁷ G. Wagner and H. Florstedt, *Pharmazie* **25**, 144 (1970).

²³⁸ G. Wagner and D. Göbel, *Z. Chem.* **10**, 265 (1970).

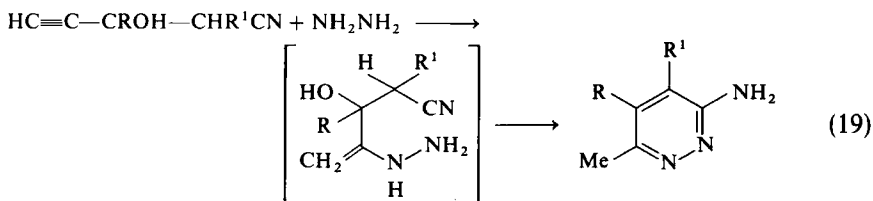
²³⁹ G. Wagner and D. Göbel, *Z. Chem.* **10**, 433 (1970).

²⁴⁰ G. Wagner and D. Göbel, *Z. Chem.* **11**, 105 (1971).

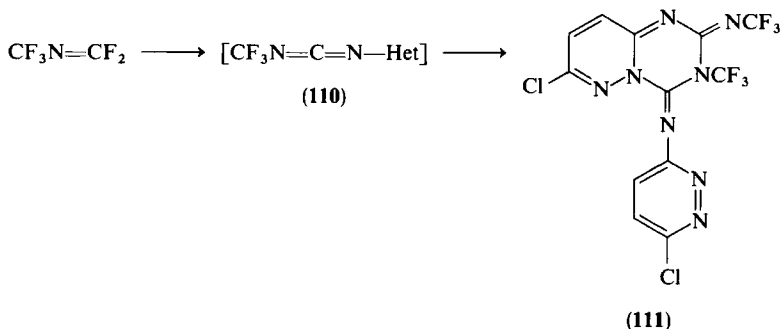
Similarly, *N*-tetrahydrofuranyl and *N*-tetrahydropyranyl and -thiopyranyl derivatives of 3-pyridazinones were prepared,²⁵⁰ and their acid hydrolysis was investigated.²⁵¹

G. MISCELLANEOUS METHODS

In a new approach 3-aminopyridazines are formed from acetylenic hydroxynitriles that add hydrazine and subsequently cyclize [Eq. (19)].^{252,253} The reaction may also form pyrazolines or pyrazoles, depending on the starting nitrile.



Perfluoroazapropene reacts with heteroaromatic amines to give carboimides **110**. In the case of 3-amino-6-chloropyridazine, this imide dimerizes



²⁴¹ G. Wagner and D. Göbel, *Pharmazie* **27**, 433 (1972).

²⁴² G. Wagner and D. Göbel, *Pharmazie* **28**, 184 (1973).

²⁴³ D. Heller and G. Wagner, *Z. Chem.* **10**, 111 (1970).

²⁴⁴ D. Heller and G. Wagner, *Z. Chem.* **11**, 253 (1971).

²⁴⁵ D. Heller and G. Wagner, *Z. Chem.* **11**, 385 (1971).

²⁴⁶ D. Heller and G. Wagner, *Pharmazie* **28**, 641 (1973).

²⁴⁷ P. Nuhn and G. Wagner, *J. Prakt. Chem.* **312**, 97 (1970).

²⁴⁸ D. Heller and G. Wagner, *Z. Chem.* **10**, 114 (1970).

²⁴⁹ D. Heller and G. Wagner, *Pharmazie* **30**, 207 (1975).

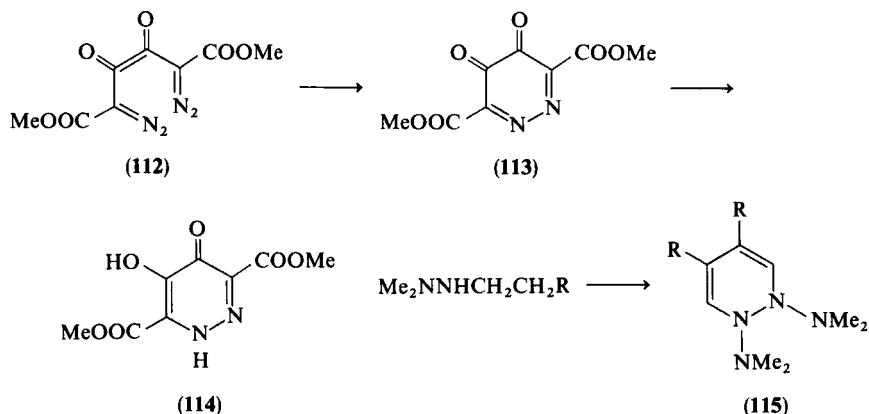
²⁵⁰ H. Kühmstedt and G. Wagner, *Arch. Pharm. (Weinheim)* **301**, 660 (1968).

²⁵¹ H. Kühmstedt and G. Wagner, *Arch. Pharm. (Weinheim)* **302**, 213 (1969).

²⁵² K. G. Golodova, S. I. Yakimovich, and F. Ya. Pervcev, *Khim. Geterotsikl. Soedin.*, 131 (1972).

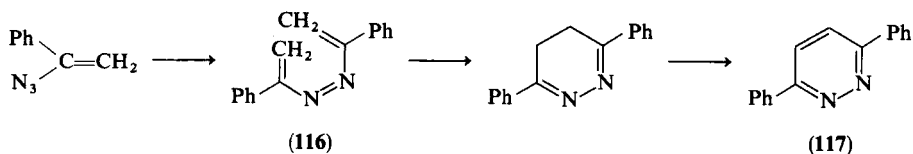
²⁵³ K. G. Golodova, S. I. Yakimovich, and F. Ya. Pervcev, *Zh. Org. Khim.* **8**, 2488 (1972).

to **111**.²⁵⁴ Dimethyl 2,5-bisdiazo-4,5-diketoadipate (**112**) is transformed into a pyridazine derivative (**114**), probably via the intermediate **113**.²⁵⁵



Oxidation of 2-substituted 1,1-dimethyl-2-ethylhydrazines with mercuric oxide gives products assigned the pyridazine structures **115**, accompanied by pyrazines.²⁵⁶ From *cis*-dibenzoylstilbene oxide and *p*-tosylhydrazine, five products were obtained, among them tetraphenylpyridazine in 6% yield.²⁵⁷

After a month at room temperature, α -styryl azide is transformed into a mixture of 2-phenylazirine and 2,5-diphenylpyrrole, along with a small amount of 3,6-diphenylpyridazine.²⁵⁸ The formation of the pyridazine is explained by reaction of two molecules of the azide to give the azo compound **116**, with subsequent ring closure and aromatization to **117**. Later, the 4,5-dihydro intermediate was identified in the reaction mixture.²⁵⁹ Similarly, 2-pyridylvinylazide decomposes spontaneously to give a pyrrole derivative and 3,6-bis(2-pyridyl)pyridazine in low yield.²⁶⁰



²⁵⁴ W. T. Flowers, R. Franklin, R. N. Haszeldine, and R. J. Perry, *Chem. Commun.*, 567 (1976).

²⁵⁵ C. W. Bird, C. K. Wong, D. Y. Wong, and F. L. K. Koh, *Tetrahedron* **32**, 269 (1976).

²⁵⁶ S. A. Giller, A. V. Eremeev, I. Kalvinsh, V. G. Semenikhina, E. Liepinsh, T. Kupch, and I. S. Yankovskaya, *Khim. Geterotsikl. Soedin.*, 396 (1976).

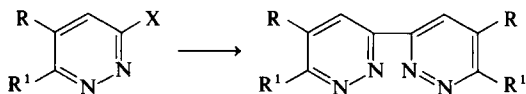
²⁵⁷ A. Padwa and M. Rostoker, *Tetrahedron Lett.*, 281 (1968).

²⁵⁸ J. H. Boyer, W. E. Krueger, and R. Modler, *Tetrahedron Lett.*, 5979 (1968).

²⁵⁹ F. P. Woerner and H. Reimlinger, *Chem. Ber.* **103**, 1908 (1970).

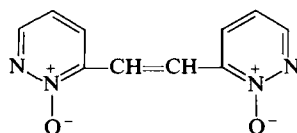
²⁶⁰ V. Nair and K. H. Kim, *J. Heterocycl. Chem.* **13**, 873 (1976).

3,3'-Bipyridazines (118) were obtained from 3-halopyridazines and hydrazine in the presence of Pd CaCO₃. 4-Substituted derivatives do not react, a fact ascribed to steric hindrance.^{261,262} The corresponding *N*-oxides react less readily to give 3,3'-bipyridazine di-*N*-oxides.²⁶² Also bis(3-pyridazinyl)ethenes and their *N*-oxides were prepared: for example, 3-formylpyridazine-2-oxide, when condensed with 3-methylpyridazine-2-oxide, affords 119,²⁶³ which, when deoxygenated and treated with hydrogen peroxide, is transformed into the isomeric 1,1'-dioxide.



X = Cl, Br

(118)



(119)

Recently it has been established that pyridazines can be formed by enzymic catalysis. For example, pyridazinones are formed from γ -glutamyl hydrazones of α -keto acids in the presence of liver glutamine transaminase, or from γ -glutamyl hydrazide in the presence of L-amino acid oxidase.²⁶⁴

Various ¹⁴C- and ³H-labeled pyridazines were prepared by standard procedures.²⁶⁵⁻²⁶⁸

III. Reactions

A. PROTONATION, N-ALKYLATION, N-OXIDATION, AND N-AMINATION

The reaction rates for quaternization of pyridazines provide a measure of the steric effect of alkyl groups.²⁶⁹ Rates for 3,6-dialkylpyridazines with methyl iodide show that the product distribution is kinetically controlled and is solvent dependent. Moreover, steric effects of substituents prevail

²⁶¹ H. Igeta, T. Tsuchiya, M. Nakajima, and H. Yokogawa, *Tetrahedron Lett.*, 2359 (1969).

²⁶² H. Igeta, T. Tsuchiya, M. Nakajima, C. Okuda, and H. Yokogawa, *Chem. Pharm. Bull.* **18**, 1228 (1970).

²⁶³ H. Igeta, T. Tsuchiya, C. Kaneko, and S. Suzuki, *Chem. Pharm. Bull.* **21**, 125 (1973).

²⁶⁴ A. J. L. Cooper and A. Meister, *J. Biol. Chem.* **248**, 8489 (1973).

²⁶⁵ T. F. Burger, *J. Labelled Comp.* **4**, 262 (1968).

²⁶⁶ N. Drescher and T. F. Burger, *Bull. Environ. Contam. Toxicol.* **5**, 79 (1970).

²⁶⁷ L. Pichat, J. P. Beaucourt, F. Krausz, and C. Moulineau, *J. Labelled Comp. Radiopharm.* **12**, 347 (1976).

²⁶⁸ A. Unverricht, G. Simon, and H. R. Schuette, *Z. Chem.* **16**, 442 (1976).

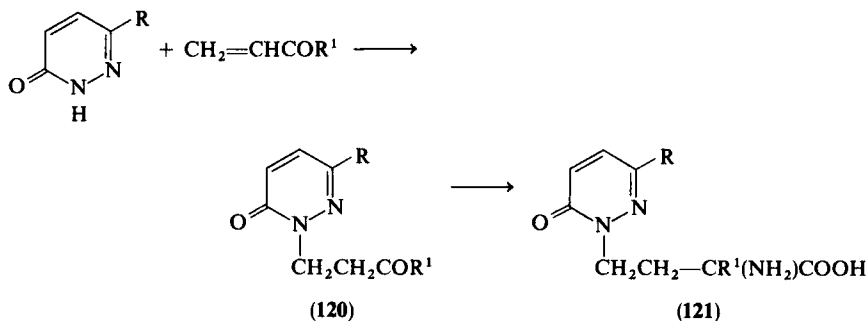
²⁶⁹ R. Gallo, M. Chanon, H. Lund, and J. Metzger, *Tetrahedron Lett.*, 3857 (1972).

over electronic ones.²⁷⁰ The behavior of some pyridazines on protonation has been examined.²⁷¹

Relative rates have been determined for the competitive methylations and also acetylations of azines. Pyridazine reacts faster than pyridines in both reactions; this is interpreted in terms of pair-pair electron repulsion and the α -effect.²⁷² An additivity approach provides reasonable predictions of isomer ratios of quaternization products of pyridazine and other azines.²⁷³ Reinvestigation of the quaternization of various amino- and diamino-pyridazines with methyl iodide shows that both 1- and 2-methyl derivatives were usually formed.²⁷⁴ 3-Amino-6-chloropyridazine forms N_2 -quaternary salts with α - and β -halo esters and 1,4-dibromobutane, but with 1,2-dibromoethane or 1,3-dibromopropane bicyclic products, are formed.²⁷⁵ Protonation and quaternization of 1,4,5,6-tetrahydropyridazines takes place at position 1, this being the more basic nitrogen.²⁷⁶

Diquaternization fails with alkyl halides but takes place with oxonium salts as alkylating agents.²⁷⁷ In this manner the reduced nucleophilicity of the second nitrogen upon monoquaternization, combined with the steric hindrance, is overcome.

Cyanoethylation of pyridazines and related N-alkylations are described.²⁷⁸ The Michael-type addition of maleic hydrazide or related pyridazinones with α,β -unsaturated carbonyl compounds give N-substitution products (120). These can be converted via hydantoins or by Bucherer



²⁷⁰ H. Lund and V. Lund, *Acta Chem. Scand.* **27**, 383 (1973).

²⁷¹ H. S. Isbell and A. J. Fatiadi, *Carbohydr. Res.* **11**, 303 (1969).

²⁷² J. A. Zoltewicz and L. W. Deady, *J. Am. Chem. Soc.* **94**, 2765 (1972).

²⁷³ J. A. Zoltewicz and L. W. Deady, *Tetrahedron* **28**, 1983 (1972).

²⁷⁴ G. B. Barlin, *J.C.S. Perkin I*, 1424 (1976).

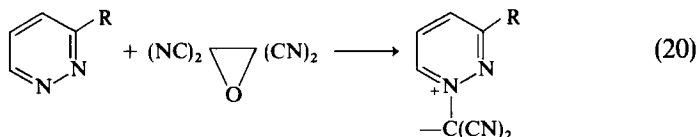
²⁷⁵ S. Ostroveršnik, B. Stanovnik, and M. Tišler, *Croat. Chem. Acta* **41**, 135 (1969).

²⁷⁶ J. L. Aubagnac, J. Elguero, R. Jacquier, and R. Robert, *C.R. Acad. Sci., Ser. C* **270**, 1829 (1970).

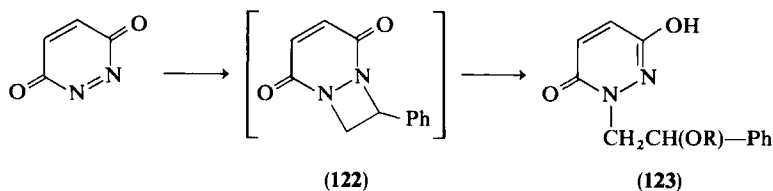
²⁷⁷ T. J. Curphey and K. S. Prasad, *J. Org. Chem.* **37**, 2259 (1972).

²⁷⁸ A. A. Sayed, H. Jahine, H. A. Zaher, and O. Sherif, *Indian J. Chem.* **13**, 1142 (1975).

synthesis into the corresponding amino acids (121).²⁷⁹ Pyridazines react also with tetracyanoethylene oxide to give the dicyanomethylides (Eq. 20).^{280,281} Similarly, pyridazine hydrobromide adds acrylamide to give the *N*-substituted quaternary salt.²⁸²



The diazaquinone, obtained from maleic hydrazide by oxidation, undergoes cycloaddition with styrene to give an unstable [2 + 2]-cycloadduct (122) which is cleaved in the presence of hydroxylic solvents to 123.^{283,284} 3,6-Bistrimethylsilyloxypyridazine gives with 2-chlorotetrahydrofuran or -pyran 1-tetrahydrofuranyl- or -pyranyl derivatives of maleic hydrazide.²⁸⁵ Pyridazinones, when treated with derivatives of ethenesulfonic acid, give *N*-sulfonylethyl derivatives, but with substituted sulfonylchlorides *O*-sulfonylation occurs.²⁸⁶



N-Oxidation of pyridazine with hydrogen peroxide and in the presence of sodium tungstate gives the *N*-oxide in low yield.²⁸⁷ Peroxydichloromaleic acid is an efficient reagent for the preparation of pyridazine *N*-oxides²⁸⁸ and polyhalogenated pyridazines are best *N*-oxidized with a mixture of hydrogen peroxide, concentrated sulfuric acid, and acetic acid or trifluoroacetic acid.^{289,290} Some 3-aminopyridazines were transformed in a single

²⁷⁹ S. Kamiya and A. Nakamura, *Chem. Pharm. Bull.* **15**, 949 (1967).

²⁸⁰ Y. Kobayashi, T. Kutsuma, and K. Morinaga, *Chem. Pharm. Bull.* **19**, 2106 (1971).

²⁸¹ T. Sasaki, K. Kanematsu, Y. Yukimoto, and S. Ochiai, *J. Org. Chem.* **36**, 813 (1971).

²⁸² A. Le Berre and A. Delacroix, *Bull. Soc. Chim. Fr.*, 640 (1973).

²⁸³ M. Lora-Tamayo, P. Navarro, and J. L. Soto, *Justus Liebigs Ann. Chem.* **748**, 96 (1971).

²⁸⁴ M. Lora-Tamayo, P. Navarro, M. Pardo, and J. L. Soto, *An. Quim.* **71**, 400 (1975).

²⁸⁵ L. Ya. Avota, I. V. Turovskii, and S. A. Giller, *Khim. Geterotsikl. Soedin.*, 1545 (1973).

²⁸⁶ A. Le Berre and B. Dumaitre, *Bull. Soc. Chim. Fr.*, 4376 (1970).

²⁸⁷ Y. Kobayashi, I. Kumadaki, H. Sato, Y. Sekine, and T. Hara, *Chem. Pharm. Bull.* **22**, 2097 (1974).

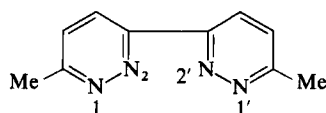
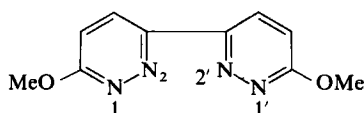
²⁸⁸ A. Pollak, M. Zupan, and B. Šket, *Synthesis*, 495 (1973).

²⁸⁹ G. E. Chivers and H. Suschitzky, *Chem. Commun.*, 28 (1971).

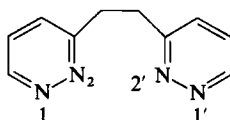
²⁹⁰ G. E. Chivers and H. Suschitzky, *J. Chem. Soc. C*, 2867 (1971).

step with 85% hydrogen peroxide in polyphosphoric acid into the otherwise not readily accessible 3-nitropyridazine 1-oxides.²⁹¹ Reactions of methylthio-pyridazines with different oxidizing agents have been studied, and in some cases both S-oxidation and N-oxidation occurs.²⁹²

N-Oxidation of 3,3'-bipyridazines is influenced by substituents in a similar way to that for pyridazines. Thus, the nitrogen atoms adjacent to an aryl or methoxy substituent are not oxidized. Thus, the 6,6'-dimethyl compound (**124**) gives with hydrogen peroxide the 1,1'-dioxide (**125**), and with peroxybenzoic acid a mixture of the monoxide (**126**) and a small amount of the dioxide (**125**). No isomeric 2-oxides were formed. Similar results were obtained with 3,3'-bipyridazine itself. On the other hand, the 6,6'-dimethoxy analog (**127**) affords the 2,2'-dioxide (**128**) with hydrogen peroxide, and a

**(124)****(125)** 1,1'-dioxide**(126)** 1-oxide**(127)****(128)** 2,2'-dioxide**(129)** 2-oxide

mixture of this compound and the 2-oxide (**129**) with peroxybenzoic acid. No isomeric 1-oxides were isolated. Oxidation of the 5,5'-dimethyl analog gave both the 2,2'- and the 1,1'-dioxide.²⁹³ The bis(pyridazinyl)ethane (**130**) affords three different N-oxides (**131–133**), the second being the main product.²⁶³

**(130)****(131)** 1,1'-dioxide**(132)** 1,2'-dioxide**(133)** 2,2'-dioxide

The first syntheses of pyridazine 1,2-dioxides have been described,²²⁵ in low yield by direct N-oxidation with 50–90% hydrogen peroxide in acetic acid.²⁹⁴ The dioxides are fairly resistant to deoxygenation with phosphorus trichloride.

²⁹¹ A. Pollak, B. Stanovnik, and M. Tišler, *J. Org. Chem.* **35**, 2478 (1970).

²⁹² T. Segal, A. Pollak, B. Stanovnik, and M. Tišler, *J. Org. Chem.* **38**, 3307 (1973).

²⁹³ H. Igeta, T. Tsuchiya, C. Okuda, and H. Yokogawa, *Chem. Pharm. Bull.* **18**, 1340 (1970).

²⁹⁴ M. Nakadate, S. Sueyoshi, and I. Suzuki, *Chem. Pharm. Bull.* **18**, 1211 (1970).

N-Amination of heterocycles disclosed useful synthons, the N-amino-heterocycles. Several pyridazines were transformed by hydroxylamine-*O*-sulfonic acid into the corresponding 1-aminopyridazinium derivatives.²⁹⁵ Substituted pyridazines, like 3-methyl-, or 3-methyl-6-methoxypyridazine were aminated only at N₂,²⁹⁵ but 3-methoxypyridazine gives the 1-amino derivative.²⁸⁰ *O*-Mesitylenesulfonylhydroxylamine is an efficient reagent for N-amination, and 3-aminopyridazines give the corresponding N-amino salts in high yields.²⁹⁶

B. SUBSTITUTIONS AT THE PYRIDAZINE RING

Many studies on electrophilic and nucleophilic reactions of pyridazines and pyridazine N-oxides show their marked similarity to those of pyridines and their N-oxides. There are, however, some differences in nucleophilic substitution of pyridazine N-oxides, position β to the N-oxide group being more reactive than α - and γ -positions.

Pyridazines are known to be quite unreactive toward electrophilic attack at ring carbons because of the large deactivation by the two ring nitrogens. Acid-catalyzed hydrogen exchange on pyridazines was studied by Katritzky and Pojarlieff.²⁹⁷ Depending on the acidity, 4-aminopyridazine exchanges either the 5-proton or the 3- and 6-protons. In deuteriosulfuric acid it exchanges as the conjugate acid at the 5-position, the exchange being competitive with hydrolysis to pyridazin-4(1*H*)-one. In neutral or alkaline solution the 3- and 6-protons of 4-aminopyridazine are exchanged at approximately equal rates, via the ylid mechanism. Pyridazin-3- and -4-ones also exchange in acid solution at position 5. To compare rate constants for acid-catalyzed hydrogen exchange, extrapolation to pH 0 and 100°C was proposed.²⁹⁸ Deuterium exchange with D₂O was most effective in the presence of a platinum catalyst.²⁹⁹

Deuterodeprotonation of pyridazine in CH₃OD—CH₃ONa was followed by NMR, and the relative rates at positions 3,6:4,5 were determined as 1:4. The pattern of activation by the annular nitrogen was established as para ~ meta >> ortho; a proposed explanation for this unusual order involves pair-pair electron repulsion between the nitrogen and carbanion and de-

²⁹⁵ K. Kasuga, M. Hirobe, and T. Okamoto, *Chem. Pharm. Bull.* **22**, 1814 (1974).

²⁹⁶ Y. Tamura, J. H. Kim, and M. Ikeda, *J. Heterocycl. Chem.* **12**, 107 (1975).

²⁹⁷ A. R. Katritzky and I. Pojarlieff, *J. Chem. Soc. B*, 873 (1968).

²⁹⁸ A. El-Anani, J. Banger, G. Bianchi, S. Clementi, C. D. Johnson, and A. R. Katritzky, *J.C.S. Perkin II*, 1065 (1973).

²⁹⁹ G. E. Calf, J. L. Garnett, and V. A. Pickles, *Aust. J. Chem.* **21**, 961 (1968).

creased s-character of the ortho CH-bond.³⁰⁰ Studies on the base-catalyzed deuterium exchange on 3-hydroxypyridazine 1-oxide showed that in pyridazin-3(2H)-one the 3-oxo group much decreases the reactivity, whereas N-oxygenation accelerates the exchange considerably at positions 4 and 6.³⁰¹

3-Hydroxypyridazine 1-oxide is readily brominated to give the 4,6-dibromo derivative.³⁰¹ This is another example of α - and γ -activation for electrophilic substitution by an N-oxide group since the des-N-oxide does not react. Chlorination proceeds similarly, but upon nitration only the 4-nitro derivative is formed.³⁰² 5-Hydroxypyridazine 1-oxide is also brominated to give the 4,6-dibromo derivative; if position 6 is blocked, the corresponding 4-bromo derivative is formed.³⁰³ 1,2-Disubstituted 5-bromopyridazine-3,6-diones are brominated to 4,5-dibromo compounds.³⁰⁴

Several 4-amino-3,6-disubstituted pyridazines were nitrated with fuming nitric acid to give the 5-nitro derivatives in good yield.³⁰⁵ Pyridazine N-oxides are relatively easily nitrated with mixed acid to give the 4-nitro derivatives.^{306,307} If this position is blocked, as with 3,6-dimethyl-4-hydroxypyridazine 1-oxide, the 5-nitro derivative is formed.³⁰⁸ Nitration of 3-methoxy-5-methylpyridazine gives the 6-nitro, 4-nitro, and 4,6-dinitro compounds.³⁰² 3,6-Dimethylpyridazine 1,2-dioxide gives the 4-nitro compound with nitric acid in good yield, but with benzoyl nitrate in low yield.³⁰⁹ The starting 1,2-dioxide is highly resistant to other electrophilic reactions.

Pyridazine-4(1H)-ones do not couple with aryldiazonium salts unless 3-oxo group is present.³¹⁰ Other reactions, such as mercuration³¹¹ and epoxidation, of pyridazines are described.³¹²⁻³¹⁵

³⁰⁰ J. A. Zoltewicz, G. Grahe, and C. L. Smith, *J. Am. Chem. Soc.* **91**, 5501 (1969).

³⁰¹ H. Igeta, M. Yamada, Y. Yoshioka, and Y. Kawazoe, *Chem. Pharm. Bull.* **15**, 1411 (1967).

³⁰² H. Igeta, T. Tsuchiya, M. Nakajima, T. Sekiya, Y. Kumaki, T. Nakai, and T. Nojima, *Chem. Pharm. Bull.* **17**, 756 (1969).

³⁰³ G. Okusa and M. Osada, *Yakugaku Zasshi* **88**, 479 (1968).

³⁰⁴ S. Baloniak and A. Mroczkiewicz, *Rocz. Chem.* **45**, 659 (1971).

³⁰⁵ M. Yanai, T. Kinoshita, S. Takeda, M. Sadaki, and H. Watanabe, *Chem. Pharm. Bull.* **18**, 1680 (1970).

³⁰⁶ P. D. Cook and R. N. Castle, *J. Heterocycl. Chem.* **10**, 551 (1973).

³⁰⁷ M. Yanai, T. Kinoshita, and S. Takeda, *Chem. Pharm. Bull.* **19**, 2181 (1971).

³⁰⁸ S. Kamiya and M. Tanno, *Chem. Pharm. Bull.* **23**, 1879 (1975).

³⁰⁹ I. Suzuki and S. Sueyoshi, *Yakugaku Zasshi* **93**, 59 (1973) [*CA* **78**, 111238 (1973)].

³¹⁰ H. G. O. Becker, H. Böttcher, G. Fischer, H. Rückauf, and S. Saphon, *J. Prakt. Chem.* **312**, 591 (1970).

³¹¹ Yu. S. Shabarov, L. D. Sychkova, A. N. Kalinichenko, and R. Ya. Levina, *Zh. Obshch. Khim.* **41**, 1599 (1971).

³¹² Yu. S. Shabarov, L. D. Sychkova, T. Ya. Derevyanko, and R. Ya. Levina, *Dokl. Akad. Nauk SSSR* **198**, 859 (1971).

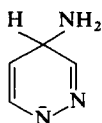
³¹³ Yu. S. Shabarov and L. D. Sychkova, *Zh. Obshch. Khim.* **42**, 2285 (1972).

³¹⁴ Yu. S. Shabarov and L. D. Sychkova, *Zh. Obshch. Khim.* **42**, 2288 (1972).

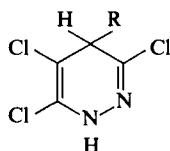
³¹⁵ Yu. S. Shabarov and L. D. Sychkova, *Zh. Obshch. Khim.* **43**, 883 (1973).

Zoltewicz and Helmick provided NMR evidence for structure **134**, the anionic sigma-complex formed by the addition of pyridazine to alkali amide in ammonia.³¹⁶

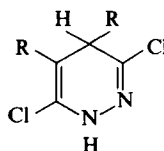
Studies on the addition of Grignard reagents to pyridazines and pyridazinium salts have continued; 4- or 5-substituted more or less unstable dihydropyridazines are formed.³¹⁷⁻³²³ The Grignard reaction involves a nucleophilic attack at one of the electron-deficient positions, followed by electron shift to give a 1,2- 1,4- or 1,6-addition. In general, 1,4-addition is predominant. Several methods of dehydrogenation into the corresponding pyridazines have been used. A study of addition of *t*-butylmagnesium chloride to 4-*t*-butyl-3,6-dimethoxypyridazine, followed by water, revealed that the initial 1,4-dihydropyridazine undergoes acid-catalyzed prototropic shifts, first to *cis*-4,5-dihydro- and, second, to *trans*-4,5-dihydropyridazine.^{324,325} 4,6-Dihydro-6-substituted pyridazines give 3,6- or 3,4,6-substituted products,^{319,326} and 4,5-dihydro-4,6-disubstituted pyridazines give 3,4,6-trisubstituted or 4,5,6-trisubstituted products.³²⁷ 1-Methyl-3,6-bisdimethylaminopyridazinium iodide gives 4-substituted 4,5-dihydro compounds.³²³ The reaction of 3,4,6-trichloropyridazine is more complex. With



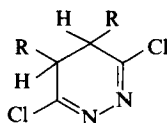
(134)



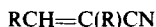
(135)



(136)



(137)



(138)

³¹⁶ J. A. Zoltewicz and L. S. Helmick, *J. Am. Chem. Soc.* **94**, 682 (1972).

³¹⁷ L. Avellen, I. Crossland, and K. Lund, *Acta Chem. Scand.* **21**, 2104 (1967).

³¹⁸ L. Avellen and I. Crossland, *Acta Chem. Scand.* **23**, 1887 (1969).

³¹⁹ F. G. Baddar, M. H. Nosseir, N. L. Doss, and N. N. Messiha, *J.C.S. Perkin I*, 1091 (1972).

³²⁰ I. Crossland and E. Kelstrup, *Acta Chem. Scand.* **22**, 1669 (1968).

³²¹ I. Crossland and H. Kofod, *Acta Chem. Scand.* **24**, 751 (1970).

³²² A. K. Fateen and N. A. K. Shams, *J. Chem. U.A.R.* **11**, 301 (1968).

³²³ E. Kelstrup, *Acta Chem. Scand.* **23**, 1797 (1969).

³²⁴ I. Crossland, *Acta Chem. Scand.* **26**, 3257 (1972).

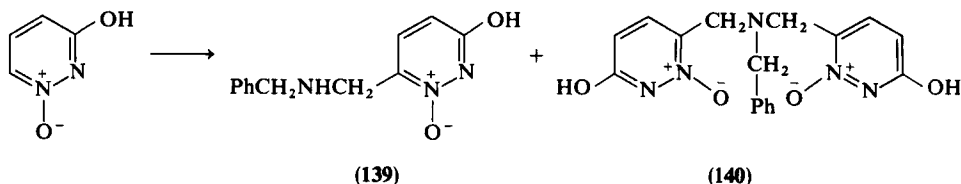
³²⁵ I. Crossland, *Acta Chem. Scand.* **26**, 4183 (1972).

³²⁶ M. A. F. Elkashef, K. M. Mokhtar, and F. M. Abdel-Moti, *Indian J. Chem.* **7**, 1098 (1969).

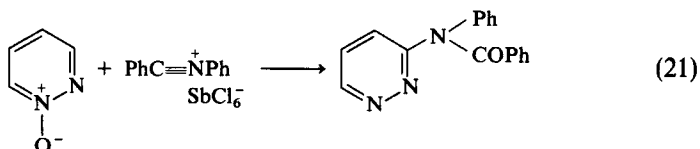
³²⁷ F. G. Baddar, N. Latif, and A. A. Nada, *J. Indian Chem. Soc.* **51**, 618 (1974).

t-butylmagnesium chloride a mixture of 4-*t*-butyl (135) and 4,5-di-*t*-butyl 1,4-dihydro derivatives (136) was obtained together with a small amount of the 4,5-di-*t*-butyl-4,5-dihydro isomer (137) and an open-chain product, 4,4-dimethyl-2-*t*-butyl-2-pentenitrile (138).³²⁸

There are further reports on the Mannich reaction on pyridazines.^{329,330} 3-Hydroxypyridazine 1-oxide is substituted at position 6 (139), and as minor product the derivative 140 is formed. If position 6 is blocked, substitution takes place at position 4.³³¹⁻³³⁴ 5-Hydroxypyridazine 1-oxide is similarly substituted at position 6,^{331,335} or, if this is blocked at position 4.^{335,336} If the hydrohalide salt of the secondary amine is used in the reaction, 3-hydroxypyridazine 1-oxide is transformed into a 6-halopyridazin-3(2*H*)-one.³³⁷



Pyridazine 1-oxide is acylaminated with *N*-phenylbenzonitrilium hexachloroantimonate to give 3-*N*-benzoylanilinopyridazine [Eq. (21)].³³⁸ A new



alkylation for pyridazines with nitroethane or nitromethane in the presence of a base has been developed.³³⁹ The conversion of 141 with potassium cyanide into the cyano derivative 142, with elimination of methanol, is a new example³⁴⁰ of a reaction described by Ochiai in 1945.

³²⁸ I. Crossland, *Acta Chem. Scand.* **22**, 2700 (1968).

³²⁹ E. Domagalina, I. Kurpiel, and N. Koktysz, *Rocz. Chem.* **43**, 775 (1969).

³³⁰ J. Strumillo, *Acta Pol. Pharm.* **32**, 287 (1975).

³³¹ S. Kamiya, G. Okusa, M. Osada, M. Kumagai, A. Nakamura, and K. Koshinuma, *Chem. Pharm. Bull.* **16**, 939 (1968).

³³² S. Kamiya and G. Okusa, *Chem. Pharm. Bull.* **21**, 1510 (1973).

³³³ G. Okusa, S. Kamiya, and T. Itai, *Chem. Pharm. Bull.* **15**, 1172 (1967).

³³⁴ G. Okusa, M. Osada, and S. Kamiya, *Chem. Pharm. Bull.* **15**, 1733 (1967).

³³⁵ G. Okusa and S. Kamiya, *Chem. Pharm. Bull.* **16**, 142 (1968).

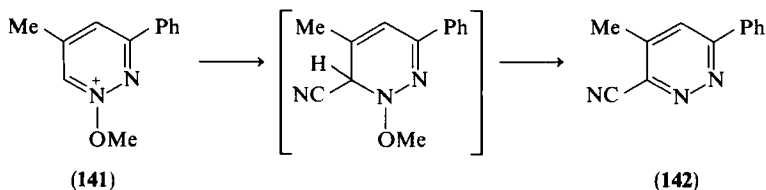
³³⁶ S. Kamiya and M. Tanno, *Chem. Pharm. Bull.* **23**, 923 (1975).

³³⁷ S. Kamiya, G. Okusa, and H. Hirakawa, *Chem. Pharm. Bull.* **18**, 632 (1970).

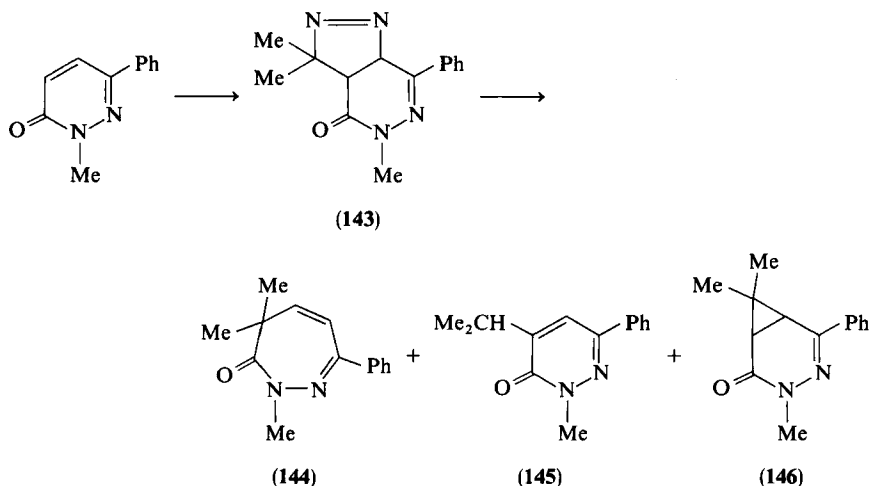
³³⁸ R. A. Abramovitch, R. B. Rogers, and G. M. Singer, *J. Org. Chem.* **40**, 41 (1975).

³³⁹ M. Yanai, S. Takeda, and M. Nishikawa, *Heterocycles* **4**, 1331 (1976).

³⁴⁰ G. Leclerc and C. G. Wermuth, *Bull. Soc. Chim. Fr.*, 1752 (1971).



The dipolar cycloaddition of 2-diazopropane to 1-methyl-3-phenylpyridazin-6-one proceeds at 0°C via an unstable cycloadduct (**143**), which is thermally decomposed to **144** as the main product, together with **145** and **146**.³⁴¹ A cycloadduct is also formed between ergosteryl acetate and the diazaquinone formed from maleic hydrazide.³⁴²



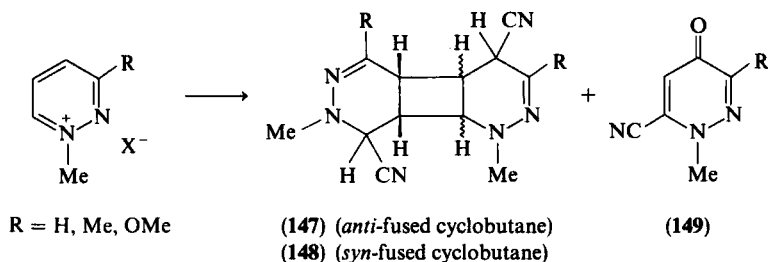
1-Methylpyridazinium salts are dimerized by the action of cyanide ion. Two kinds of dimer (**147**, **148**), sometimes together with a small amount of **149**, were obtained, and a mechanism for this transformation is proposed.^{343,344} 4- and 5-Substituted pyridazines do not form dimers, and 3,6-disubstituted pyridazines give 4-cyano- or 4,5-dicyano derivatives. 3-Phenylpyridazine gives 4-cyano-1,4-dihydro-1-methyl-3-phenylpyridazine as the main product.³⁴⁴ However, quaternary salts of 3,3'-bipyridazines and their N-oxides add cyanide ion at the ring to give the dihydro compounds. The cyano group attacks at the γ -position to the N-methyl group (giving **150**)

³⁴¹ M. Franck-Neumann and G. Leclerc, *Tetrahedron Lett.*, 1063 (1969).

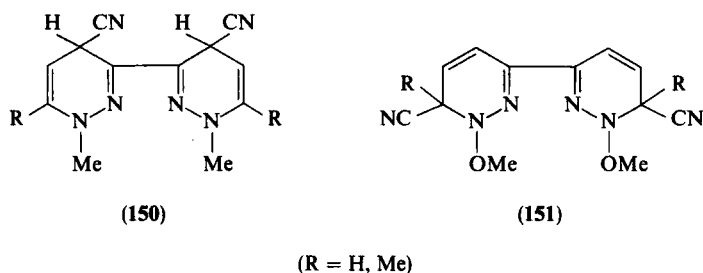
³⁴² P. E. Goerghiou and G. Just, *J.C.S. Perkin I*, 888 (1973).

³⁴³ H. Igeta, T. Tsuchiya, and C. Kaneko, *Tetrahedron Lett.*, 2883 (1971).

³⁴⁴ C. Kaneko, T. Tsuchiya, and H. Igeta, *Chem. Pharm. Bull.* **21**, 1764 (1973).



in bipyridazines, but at the α -position to the N-oxide group in the 1,1'-dioxide (forming **151**).³⁴⁵



Pyridazine N-oxides and ylids react with benzyne (Scheme 3). Pyridazine N-oxide gives a mixture of the 1-benzoxepin (**153**) and arylpyridazine (**154**) via the 1,3-cycloadduct (**152**).³⁴⁶ N-Acetylpyridazinium imide forms an isolable cycloadduct (**155**) which is transformed by heat or sodium methylate into **156** and **157**. The cycloadduct (**158**) from pyridazinium dicyanomethylide under similar reaction conditions is aromatized to **159**.³⁴⁶

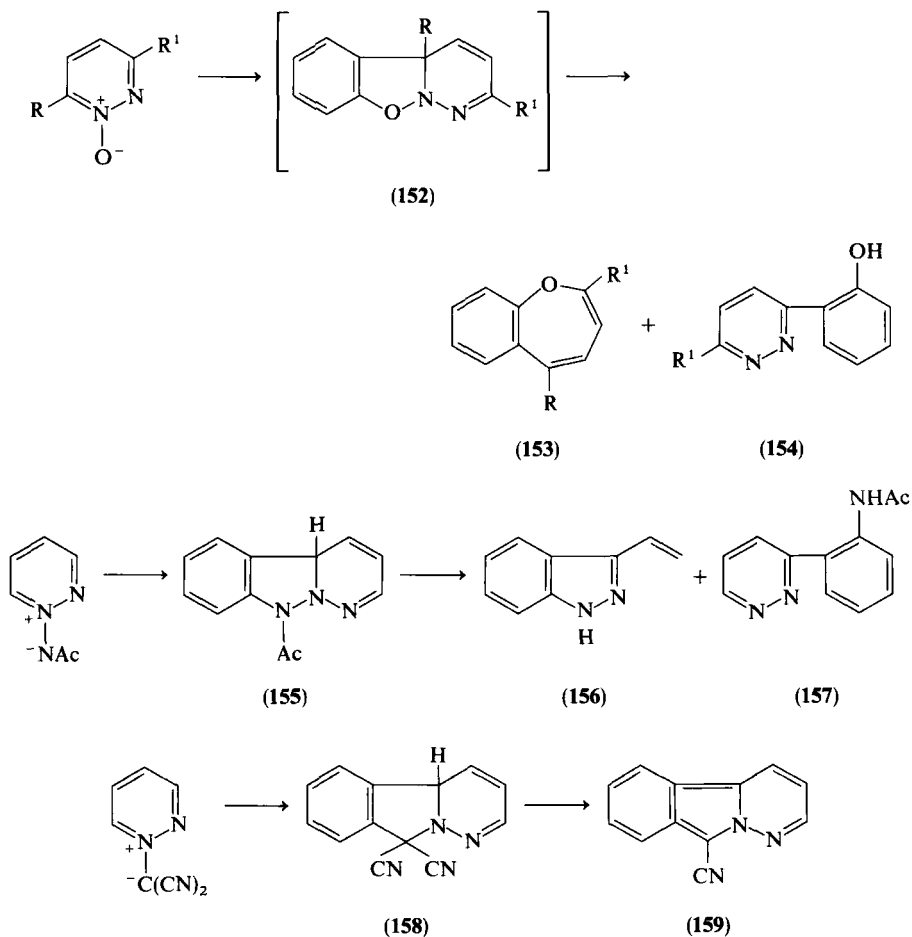
6-Phenylpyridazin-3-ones react with dimethylsulfonium methylide to give the N-methyl compounds, but with N-substituted analogs addition to the C₄-C₅ double bond occurs with the formation of a fused cyclopropane ring.³⁴⁷ A similar reaction via these bicyclo compounds enables the introduction of a C-methyl group into the pyridazine ring. A pyridazinone and ethyl chloroacetate in the presence of NaH gives **160**, which upon saponification to **161** and decarboxylation gives a mixture of the isomeric methyl compounds **162** and **163**.³⁴⁸

³⁴⁵ H. Igeta, T. Tsuchiya, C. Okuda, and H. Yokogawa, *Chem. Pharm. Bull.* **19**, 1297 (1971).

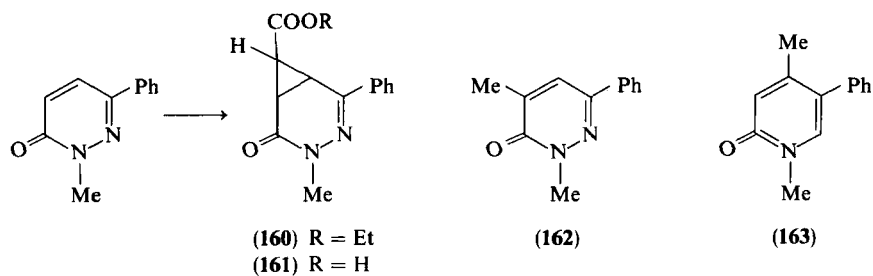
³⁴⁶ H. Igeta, H. Arai, H. Hasegawa, and T. Tsuchiya, *Chem. Pharm. Bull.* **23**, 2791 (1975).

³⁴⁷ G. Leclerc and C. G. Wermuth, *Bull. Soc. Chim. Fr.*, 4123 (1968).

³⁴⁸ G. Leclerc and C. G. Wermuth, *Bull. Soc. Chim. Fr.*, 2468 (1969).



SCHEME 3

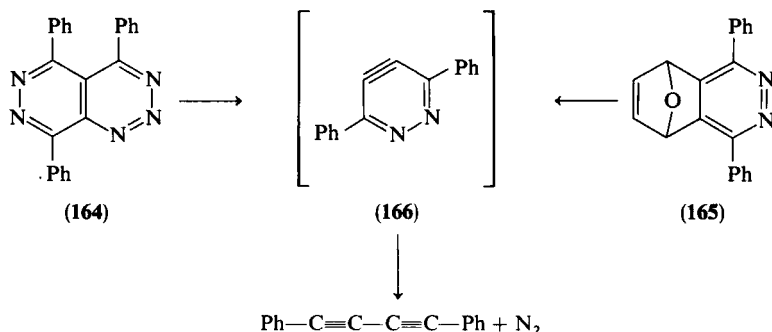


Homolytic benzylation of pyridazine yielded only the 4-benzyl derivative in acid solution, and similarly benzoylation gave mainly the 4-benzoyl and 4,5-dibenzoyl derivatives.³⁴⁹

C. REACTIONS INVOLVING FUNCTIONAL GROUPS

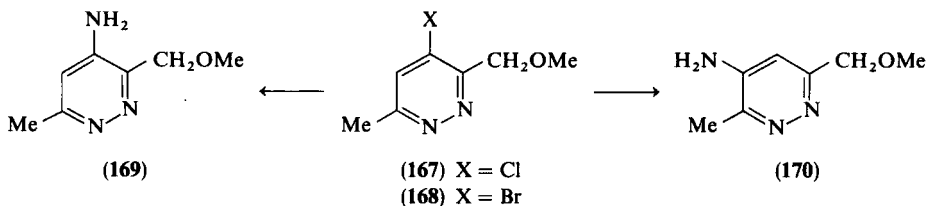
There are many examples of changing functionality at the pyridazine ring, and most of them involve halopyridazines.

A 4,5-didehydropyridazine was first postulated in 1973. Pyrolysis of either **164** or **165** proceeds most likely via 3,6-diphenyl-4,5-didehydropyridazine (**166**), which upon elimination of nitrogen gives diphenylbutadiyne (Scheme 4).^{350,351} Van der Plas and co-workers obtained evidence for a 4,5-didehydro-



SCHEME 4

pyridazine (4,5-pyridazyne) in S_N reactions. 4-Halo-3(methoxymethyl)-6-methylpyridazines (**167**, **168**) with potassium amide in liquid ammonia at -33°C give mixed 4- and 5-amino derivatives (**169**, **170**) in a 1:5 ratio which



SCHEME 5

³⁴⁹ G. Heinisch, A. Jentzsch, and M. Pailer, *Monatsh. Chem.* **105**, 648 (1974).

³⁵⁰ T. L. Gilchrist, G. E. Gymer, and C. W. Rees, *Chem. Commun.*, 819 (1973).

³⁵¹ T. L. Gilchrist, G. E. Gymer, and C. W. Rees, *J.C.S. Perkin I*, 1747 (1975).

is independent of the halogen atom (Scheme 5).³⁵² Further evidence for this hetaryne follows from the ¹³C-NMR measurements of the transformation of 4-chloro-3,6-diphenylpyridazine with potassium amide in liquid ammonia into the 4-amino compound and imino-4,4'-bis(3,6-diphenylpyridazine).³⁵³ Calculations using the extended Hückel theory predict that 4,5-didehydropyridazine is more stable than the isomeric 3,4-didehydro isomer or 3,4-didehydropyridine.³⁵⁴

There are many examples of replacement of the halogen atom in 3-halopyridazines with various nucleophiles.³⁵⁵⁻³⁶⁴ With phenols aryloxypridazines were prepared³⁶⁵⁻³⁷⁰; with a N-hydroxycarbamate the corresponding pyridazinyloxycarbamate was obtained³⁷¹ leading to several new amino- or hydrazinopyridazines.³⁷²⁻³⁷⁴

Reaction of halodiazines with *p*-nitrophenoxide ion established the following reactivity order: 4-chloropyrimidine > 4-chloropyridazine \approx 3-chloropyridazine \approx chloropyrazine.³⁷⁵ According to previous findings,

³⁵² D. E. Klinge, H. C. Van der Plas, and A. Koudijs, *Rec. Trav. Chim. Pays-Bas* **93**, 201 (1974).

³⁵³ D. E. Klinge and H. C. Van der Plas, *Rec. Trav. Chim. Pays-Bas* **95**, 34 (1976).

³⁵⁴ W. Adam, A. Grimison, and R. Hoffmann, *J. Am. Chem. Soc.* **91**, 2590 (1969).

³⁵⁵ L. I. Bigar, I. G. Novikova, and S. G. Solomonova, *Khim. Issled. Farm.*, 8 (1970) [*CA* **75**, 140784 (1971)].

³⁵⁶ T. Sasaki, K. Kanematsu, and M. Murata, *J. Org. Chem.* **36**, 446 (1971).

³⁵⁷ G. H. Singhal, P. M. Thomas, and I. C. Popoff, *J. Heterocycl. Chem.* **5**, 411 (1968).

³⁵⁸ E. Stefanescu, R. Mocanu, V. Manaila, and M. Petrovanu, *An. Stiint. Univ. "Al. I. Cuza" Iasi, Sect. Ic* **13**, 65 (1967) [*CA* **68**, 37864 (1968)].

³⁵⁹ J. Wolinski and A. Uliasz, *Acta Pol. Pharm.* **31**, 21 (1974).

³⁶⁰ J. Wolinski and A. Ilczuk, *Acta Pol. Pharm.* **32**, 307 (1975).

³⁶¹ J. Wolinski and A. Ilczuk, *Acta Pol. Pharm.* **32**, 539 (1975).

³⁶² J. Wolinski and A. Ilczuk, *Acta Pol. Pharm.* **33**, 457 (1976).

³⁶³ J. Wolinski and A. Ilczuk, *Acta Pol. Pharm.* **33**, 547 (1976).

³⁶⁴ M. Yanai, T. Kuraishi, T. Kinoshita, and M. Nishimura, *J. Heterocycl. Chem.* **7**, 465 (1970).

³⁶⁵ N. Ishikawa, K. Kuroda, and N. Onodera, *Kogyo Kagaku Zasshi* **74**, 1490 (1971) [*CA* **75**, 76709 (1971)].

³⁶⁶ T. Jojima, K. Oyamada, and S. Tamura, *Agric. Biol. Chem.* **32**, 1376 (1968).

³⁶⁷ T. Jojima, *Ann. Sankyo Res. Lab.* **24**, 121 (1972) [*CA* **78**, 159538 (1973)].

³⁶⁸ J. Schramm, E. Radlmann, H. Lohwasser, and G. Nischk, *Justus Liebigs Ann. Chem.* **740**, 169 (1970).

³⁶⁹ J. Wolinski and A. Ilczuk, *Acta Pol. Pharm.* **33**, 141 (1976).

³⁷⁰ J. Wolinski and A. Ilczuk, *Acta Pol. Pharm.* **34**, 139 (1977).

³⁷¹ T. Sheradsky, G. Salemnick, and Z. Nir, *Tetrahedron* **28**, 3833 (1972).

³⁷² E. A. Steck and L. T. Fletcher, *J. Heterocycl. Chem.* **11**, 1077 (1974).

³⁷³ E. A. Steck, R. P. Brundage, and L. T. Fletcher, *J. Heterocycl. Chem.* **12**, 1009 (1975).

³⁷⁴ M. Yanai, T. Kinoshita, S. Takeda, M. Mishimura, and T. Kuraishi, *Chem. Pharm. Bull.* **20**, 1617 (1972).

³⁷⁵ T. L. Chan and J. Miller, *Aust. J. Chem.* **20**, 1595 (1967).

1,2-disubstituted 4-bromopyridazinediones react with various nucleophiles, such as amines or alcohols, to give the cine-substituted (5-substituted) products.³⁷⁶ 3-Chloro-6-methylpyridazine reacts with 1,2,3-triazole or benzotriazole to give the N-substituted products.^{377,378}

3-Nitro-6-chloropyridazine 1-oxide reacts with nucleophiles with displacement of the 6-chlorine atom (even with acetyl bromide), except with sodium methoxide. Herer, the 3-nitro group is displaced.²⁹¹ Nucleophilic substitution with amines was investigated for various monoalkoxydihalo- or dialkoxyhalopyridazines.³⁷⁹ Normally, the chlorine atom is replaced, but in 3-chloro-4,6-dialkoxy- or 4-alkoxy-3,6-dichloropyridazines the alkoxy group may be replaced preferentially or concurrently.³⁷⁹ The 6-chlorine atom of methyl (3,6-dichloropyridazin-4-yl)-acetate was displaced by hydrazine or on hydrolysis.³⁸⁰

There are numerous investigations of the reactivity of di- and polyhalopyridazines, particularly polyfluoropyridazines. Aminolysis of 1-phenyl-4,5-dichloropyridazin-6-one has been studied in detail.³⁸¹ In this and other reactions with nucleophiles, the halogen atom at position 4 is substituted preferentially,³⁸²⁻³⁸⁴ although a mixture of 4-amino and 5-amino derivatives is formed in the reaction between 4,5-dihalopyridazin-6-ones and ammonia or amines.³⁸⁵ It has been now firmly established that displacement reactions on 3,6-dichloropyridazine 1-oxide with sulfur nucleophiles take place at position 6 in contrast to nitrogen or oxygen nucleophiles, where the 3-chlorine atom is replaced preferentially.³⁸⁶ In connection with the previously observed self-condensation of 3-chloro-6-methylpyridazine to a tricyclic product, the reaction between 3,6-dichloropyridazine and pyridine N-oxides was investigated. 3,6-Dichloropyridazine with 2-methylpyridine N-oxide at 100°–110°C affords three compounds (**171**, **172**, and **173**).³⁸⁷ With 2,6-dimethylpyridine N-oxide, an ether (**174**) is also formed. The isolation of

³⁷⁶ S. Baloniak and A. Mroczkiewicz, *Acta Pol. Pharm.* **30**, 123 (1973).

³⁷⁷ A. J. Hubert and H. Reimlinger, *Chem. Ber.* **103**, 2828 (1970).

³⁷⁸ A. J. Hubert and H. Reimlinger, *Chem. Ber.* **103**, 3811 (1970).

³⁷⁹ J. K. Landquist and S. E. Meek, *J.C.S. Perkin I*, 2735 (1972).

³⁸⁰ G. Adembri, F. De Sio, R. Nesi, and M. Scotton, *J. Heterocycl. Chem.* **13**, 1155 (1976).

³⁸¹ L. Ya. Avota, N. Ya. Ozolin, and S. A. Giller, *Latv. PSR Zinat. Akad. Vestis, Khim. Ser.*, 347 (1967) [*CA* **68**, 49555 (1968)].

³⁸² A. H. Karklinya and E. Yu. Gudriniece, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, 374 (1968) [*CA* **70**, 3996 (1969)].

³⁸³ A. H. Karklinya and E. Yu. Gudriniece, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, 560 (1968).

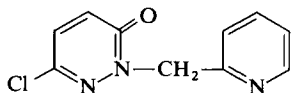
³⁸⁴ A. H. Karklinya and E. Yu. Gudriniece, *Khim. Geterotsikl. Soedin.*, 1127 (1969).

³⁸⁵ K. H. Pilgram and G. E. Pollard, *J. Heterocycl. Chem.* **14**, 1039 (1977).

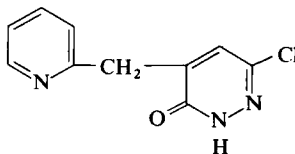
³⁸⁶ M. Ochiai, T. Okada, A. Morimota, and K. Kawakita, *J.C.S. Perkin I*, 1988 (1976).

³⁸⁷ A. Deegan and F. L. Rose, *J. Chem. Soc. C*, 2756 (1971).

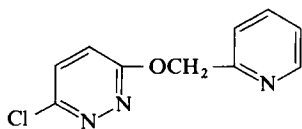
these compounds indicates two reaction courses, one involving the methyl group at the pyridine part and forming a new C—C, C—N, or C—O bond, and the other leaving this group intact. Mechanistic interpretations were proposed.



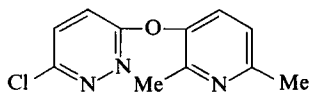
(171)



(172)



(173)



(174)

4,5-Dihalopyridazin-6-ones exchange both halogens with benzylthio groups, but in the presence of sodium amide the 5-mercapto-4-benzylthio compound is obtained.³⁸⁸ The 4,5-bismercapto compound can be prepared either by debenzylation of the 4,5-bisbenzylthio compound with AlCl_3 ^{389,390} or from the 4,5-dichloro compound and P_4S_{10} . In general, 4,5-dihalopyridazin-6-ones react with NaHS or thiolates to give 4-substituted products.^{389,391–396} However, 4,5-dichloropyridazin-6-one is reported not to exchange the 4-chlorine atom with sodium methoxide because of deprotonation at the lactam group and resulting deactivation for nucleophilic substitution. The 1-substituted analog readily gives the 4-methoxy derivative.³⁹⁷

In contrast to halopyridazine 1-oxides, 4,6-dibromo-3-hydroxypyridazine 1-oxide does not react with amines; nucleophilic substitution occurred with more potent nucleophiles, and with KHS both bromine atoms were exchanged.³⁰¹

³⁸⁸ K. Kaji, H. Mori, I. Yoshida, T. Ichii, H. Nagashima, and R. N. Castle, *Gifu Yakka Daigaku Kiyo* **17**, 66 (1967) [*CA* **70**, 28883 (1969)].

³⁸⁹ K. Kaji, M. Kuzuya, and R. N. Castle, *Chem. Pharm. Bull.* **18**, 147 (1970).

³⁹⁰ K. Kaji and M. Kuzuya, *Chem. Pharm. Bull.* **18**, 970 (1970).

³⁹¹ F. Duro, P. Condorelli, and G. Pappalardo, *Farmaco, Ed. Sci.* **32**, 173 (1977).

³⁹² M. Kuzuya and K. Kaji, *Chem. Pharm. Bull.* **18**, 2420 (1970).

³⁹³ R. F. Meyer, *J. Heterocycl. Chem.* **6**, 407 (1969).

³⁹⁴ G. Pappalardo, F. Duro, G. Scapini, and F. Vittorio, *Farmaco, Ed. Sci.* **27**, 643 (1972).

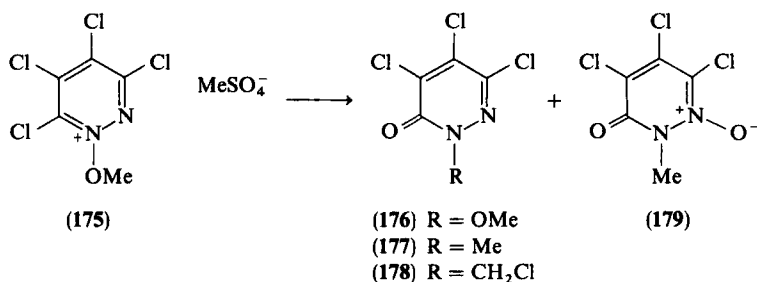
³⁹⁵ G. Pappalardo, E. Bousquet, and F. Duro, *Farmaco, Ed. Sci.* **28**, 681 (1973).

³⁹⁶ G. Scapini, F. Duro, and G. Pappalardo, *Ann. Chim. (Rome)* **58**, 709 (1968).

³⁹⁷ J. W. Mason and R. G. Salisbury, *J. Heterocycl. Chem.* **5**, 555 (1968).

Nucleophilic substitutions with alkoxides and secondary amines on halo-dialkylaminopyridazines were investigated. Alkoxides replace the 3-chlorine atom of 3,6-dichloro-4-dialkylaminopyridazines, whereas secondary amines attack the 4-chlorine.³⁹⁸ Both nucleophiles replace the 4-halogen atom of 3,4-dichloro-6-dialkylamino compounds and that at position 3 of 3,4-dichloro-5-dialkylamino compounds. No selectivity was observed with the corresponding trichloro compounds.³⁹⁸

In tri- or tetrachloropyridazines the 4-halogen atom is substituted in reactions with amines or thiols.³⁹⁹⁻⁴⁰² 3,4,5-Trichloropyridazin-6-one gives with dimethylamine a mixture of the 4- and 5-dimethylamino compounds.⁴⁰³ N-methoxy metholsulfates of some tri- and tetrachloropyridazines and their reactions with some nucleophiles were investigated.⁴⁰⁴ For example, compound **175** reacts vigorously with water to give a mixture of four different products (**176-179**): **177** is formed by thermal deoxygenation of **179**.



The reaction of polychloropyridazines with trimethylamine at room temperature gives trimethylammonium salts, which when heated in dimethylformamide, were transformed into dimethylaminopyridazines.⁴⁰⁵ For example, 3,4,6-trichloropyridazine gives a mixture of **180** and **181**, from which both isomers **182** and **183** were formed upon heating, the first being the main product (Scheme 6). Similarly, 3,4,5-trichloropyridazine gives the 5-dimethylamino derivative and tetrachloropyridazine affords a mixture of the 3-dimethylamino and 3,6-bisdimethylamino compounds. Most of these transformations are somewhat surprising if we take into account that nucleophiles usually attack first at positions 4 or 5. The course of these reactions is claimed to be governed by steric factors.⁴⁰⁵

³⁹⁸ R. S. Fenton, J. K. Landquist, and S. E. Meek, *J.C.S. Perkin I*, 2323 (1972).

³⁹⁹ I. Crossland and H. Kofod, *Acta Chem. Scand.* **21**, 2131 (1967).

⁴⁰⁰ G. S. Predvoditeleva, T. V. Kartseva, and M. N. Shchukina, *Khim. Farm. Zh.* **7**, 13 (1973).

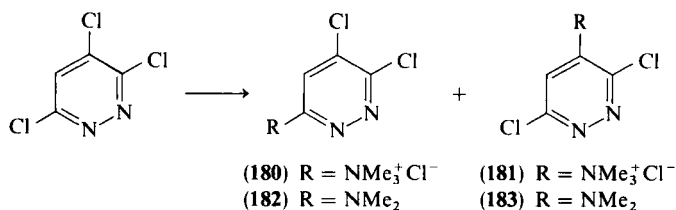
⁴⁰¹ D. S. Wise and R. N. Castle, *J. Heterocycl. Chem.* **11**, 1001 (1974).

⁴⁰² F. Yoneda and T. Ohtaka, *Yakugaku Zasshi* **88**, 1638 (1968) [*CA* **70**, 77897 (1969)].

⁴⁰³ J. K. Landquist and C. W. Thornber, *J.C.S. Perkin I*, 1114 (1973).

⁴⁰⁴ D. E. Bubblitz, *J. Heterocycl. Chem.* **9**, 471 (1972).

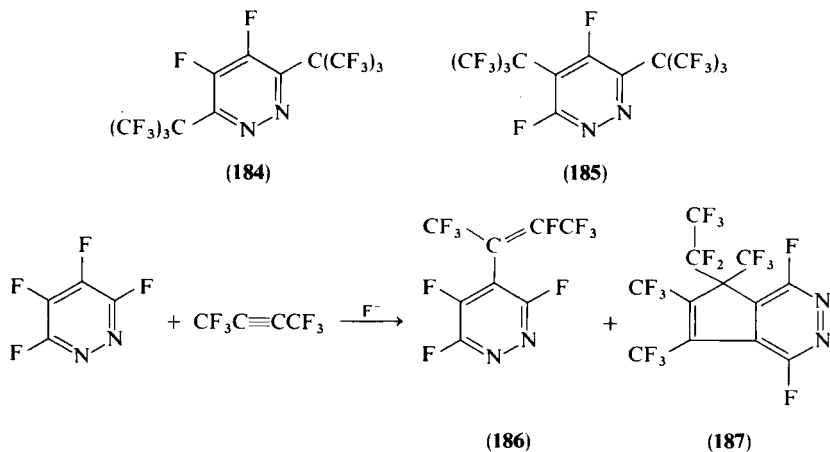
⁴⁰⁵ R. S. Fenton, J. K. Landquist, and S. E. Meek, *J. Chem. Soc. C*, 1536 (1971).



SCHEME 6

The fluoropyridazines have been intensively investigated by Musgrave and co-workers. Earlier work on nucleophilic substitutions in perfluoropyridazines has been reviewed.⁴⁰⁶ Tetrafluoropyridazine reacts with hexafluoropropene to give products formed from both kinetic and thermodynamic control of the polyfluoroalkylation, i.e., the fluoride ion-induced reaction between a fluoroolefin and an activated polyfluoroaromatic compound.⁴⁰⁷ The reaction with tetrafluoroethylene is kinetically controlled.^{408,409} Products arising only from thermodynamic control are formed, however, in the reaction with octafluoroisobutene.

Tetrafluoropyridazine, 37 times more reactive than pentafluoropyridine in the reaction with ammonia,⁴¹⁰ with octafluoroisobutene at high temperature gives exclusively perfluoro-3,6-di-*t*-butylpyridazine (184), whereas



⁴⁰⁶ W. K. R. Musgrave, *Chem. Ind. (London)*, 943 (1969).

⁴⁰⁷ R. D. Chambers, Yu. A. Cheburkov, J. A. H. MacBride, and W. K. R. Musgrave, *J. Chem. Soc. C*, 532 (1971).

⁴⁰⁸ R. D. Chambers, R. P. Corbally, M. Y. Gribble, and W. K. R. Musgrave, *Chem. Commun.*, 1345 (1971).

⁴⁰⁹ R. D. Chambers and M. Y. Gribble, *J.C.S. Perkin I*, 1405 (1973).

⁴¹⁰ R. D. Chambers, S. Partington, and D. B. Speight, *J.C.S. Perkin I*, 2673 (1974).

at lower temperature the perfluoro 4-*t*-butyl [initial attack of $(\text{CF}_3)_3\text{C}^-$ and 3,5-di-*t*-butyl derivatives (**185**) are obtained.⁴¹¹ Compound **185** is an intermediate since upon heating with cesium fluoride, it is converted into **184**. The substitution pattern is critically dependent on the olefin used, i.e., the ease of formation as well as the steric effects, in the series $(\text{CF}_3)_3\text{C}^- > (\text{CF}_3)_2\text{CF}^- > \text{CF}_3\text{CF}_2^-$.

Syntheses of several other perfluoroalkyl⁴¹² or perfluorocycloalkylpyridazines⁴¹³ are reported. With acetylenic compounds, for example with hexafluorobut-2-yne, tetrafluoropyridazine is alkylated in the presence of fluoride ion at position 4 (**186**), but in addition a bicyclic derivative (**187**) was isolated.^{410,414}

Whereas under basic conditions the fluorine atoms at positions 4 and 5 of polyfluoropyridazines are replaced, under strongly acidic conditions those at positions 3 and 6 react.⁴¹⁵ All four fluorine atoms of tetrafluoropyridazine are substituted in the reaction with ethereal hydrogen chloride at room temperature, but in aqueous sulfuric acid only the 6-fluorine atom is replaced.⁴¹⁵

Various reactions involving the hydroxy and methoxy groups have been performed. Trimethylsilylation of pyridazinones was studied,⁴¹⁶ and were synthesized phosphorothioates⁴¹⁷ and heteroaryloxypyridazines.⁴¹⁸ N-Acetyl maleic hydrazide is not obtained by the previously described procedure.^{89,419} However, with ketene an O,N-diacetyl derivative is formed that in hot ethanol gives the stable O-acetyl maleic hydrazide.⁸⁹ Maleic hydrazide reacts to give with diarylnitrilimines O-substitution products⁴²⁰ and with sulfonyl chlorides the corresponding O-sulfonyl derivatives,⁴²¹⁻⁴²³

⁴¹¹ S. L. Bell, R. D. Chambers, M. Y. Gribble, and J. R. Maslakiewicz, *J.C.S. Perkin I*, 1716 (1973).

⁴¹² R. D. Chambers, J. A. Jackson, S. Partington, P. D. Philpot, and A. C. Young, *J. Fluorine Chem.* **6**, 5 (1975).

⁴¹³ R. D. Chambers, M. Y. Gribble, and E. Marper, *J.C.S. Perkin I*, 1710 (1973).

⁴¹⁴ R. D. Chambers, W. K. R. Musgrave, and S. Partington, *Chem. Commun.*, 1050 (1970).

⁴¹⁵ R. D. Chambers, J. A. H. MacBride, and W. K. R. Musgrave, *J. Chem. Soc. C*, 2989 (1968).

⁴¹⁶ L. Ya. Avota, V. A. Pestunovich, and S. A. Giller, *Khim. Geterotsikl. Soedin.*, 990 (1975).

⁴¹⁷ T. Jojima and H. Takeshiba, *Agric. Biol. Chem.* **38**, 1169 (1974).

⁴¹⁸ V. V. Dovlatyan and N. Kh. Khachatryan, *Arm. Khim. Zh.* **24**, 51 (1971) [*CA* **75**, 20360 (1971)].

⁴¹⁹ H. Feuer and J. P. Asunskis, *J. Org. Chem.* **27**, 4684 (1962).

⁴²⁰ F. Sauter and U. Jordis, *Org. Prep. Proced. Int.* **9**, 45 (1977).

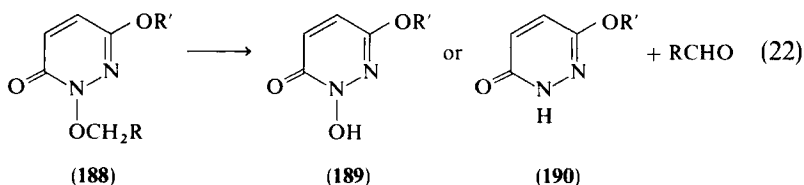
⁴²¹ G. A. Galoyan, S. G. Agbalyan, G. T. Esayan, and N. R. Postoyan, *Arm. Khim. Zh.* **20**, 531 (1967).

⁴²² G. A. Galoyan, S. G. Agbalyan, and G. T. Esayan, *Arm. Khim. Zh.* **21**, 515 (1968) [*CA* **70**, 47381 (1969)].

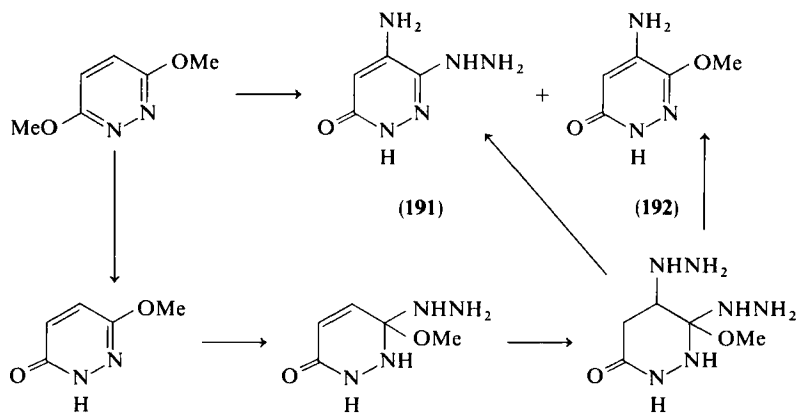
⁴²³ J. Gubin, N. Durant, R. Nasielski-Hinkens, and R. Promel, *Bull. Soc. Chim. Belg.* **82**, 371 (1973).

which react with some nucleophiles.^{424,425} With monochloroacetic acid the O-carboxymethyl derivatives were prepared.⁴²⁶

1-Alkoxy-4-pyridazine-ones are prepared from 4-hydroxy 1-oxides and alkyl iodides in the presence of silver oxide.³⁰⁸ 1-Alkoxy-4-pyridazine-6-ones (**188**), which may be regarded as esters of cyclic hydroxamic acids, when treated with alkali or amines are transformed into **189** or **190** and an aliphatic aldehyde [Eq. (22)], depending upon the 1-substituent.⁴²⁷ Acid-catalyzed hydrolysis of some 3-methoxypyridazines was also studied.⁴²⁸



3,6-Dimethoxypyridazine was claimed to react with hydrazine to give 3,6-dihydrazinopyridazine,⁴²⁹ but it is now established that a mixture of 3-hydrazino-4-aminopyridazine-6-one (**191**) and its 3-methoxy analog (**192**)



SCHEME 7

⁴²⁴ G. A. Galoyan, S. G. Agbalyan, and G. T. Esayan, *Arm. Khim. Zh.* **23**, 837 (1970) [*CA* **74**, 53698 (1971)].

⁴²⁵ G. A. Galoyan, S. G. Agbalyan, and G. T. Esayan, *Arm. Khim. Zh.* **24**, 535 (1971).

⁴²⁶ G. A. Galoyan, S. G. Agbalyan, and G. T. Esayan, *Arm. Khim. Zh.* **24**, 350 (1971) [*CA* **75**, 140785 (1971)].

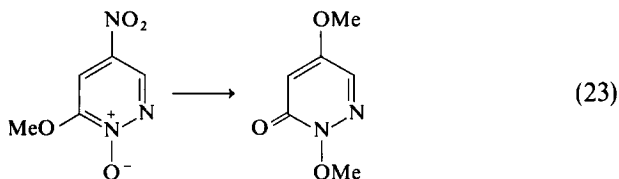
⁴²⁷ M. Yanai and M. Yamaguchi, *Chem. Pharm. Bull.* **16**, 1244 (1968).

⁴²⁸ V. S. Venturella, *J. Pharm. Sci.* **57**, 1151 (1968).

⁴²⁹ T. V. Gortinskaya and M. N. Shchukina, *Zh. Obshch. Khim.* **30**, 1518 (1960).

was formed.^{430,431} The corresponding 3,6-dichloro-, 3,6-diphenoxy-, or 3,6-dimethylthiopyridazines afford only the monohydrazino compounds.⁴³¹ This last procedure has been criticized for giving in part erratic results, and it was later found that pyridazine-3,6-bisthiouronium chloride, obtained from 3,6-dichloropyridazine and thiourea, when decomposed with sodium hydrogen carbonate, does not give 3-mercaptopyridazine-6(1*H*)-thione (dithiomaleic hydrazide), but a sulfide. A reaction mechanism involving addition and elimination has been proposed for the hydrazine reaction (Scheme 7).⁴³¹

6-Methoxy-4-nitropyridazines react with alkyl iodides at about 100°C to give esters of cyclic hydroxamic acids [Eq. (23)] resulting from methylation, demethylation, and nitro group displacement. A 6-methyl group is transformed into a cyano group by the nitrous acid produced.⁴³²



Study of the reaction between 6-chloro-3-methoxy-4-nitropyridazine 1-oxide or related compounds and methanolic ammonia or liquid ammonia to give the 3-amino compounds upon amino-demethoxylation, revealed the formation of an intermediate sigma-adduct.⁴³³ By ¹H-NMR and ¹³C-NMR spectroscopy it could be established that the sigma-adduct involved addition at the 5-C-atom.⁴³³⁻⁴³⁵

Depending upon the reaction conditions or nucleophile, the nitro or methoxy groups can be replaced in 4,6-dinitro-3-methoxypyridazine 1-oxide (**193**) (Scheme 8).^{436,437} Thus, it gives **194** with hydrochloric acid, and with a primary amine a mixture of the amino compounds **195** and **196** is obtained. With acetyl chloride, however, both nitro groups are displaced to give **197**. Nucleophiles react with compound **194** by displacing the 4-nitro group.⁴³⁶ Similarly, the dioxide **198** with hot hydrohalic acid or acetyl chloride gives **199**. With acetyl chloride at room temperature after a week, in addition to

⁴³⁰ S. Alazawe and J. A. Elvidge, *J.C.S. Perkin I*, 696 (1974).

⁴³¹ J. A. Elvidge and J. A. Pickett, *J.C.S. Perkin I*, 1483 (1972).

⁴³² M. Yanai and T. Kinoshita, *Chem. Pharm. Bull.* **16**, 1221 (1968).

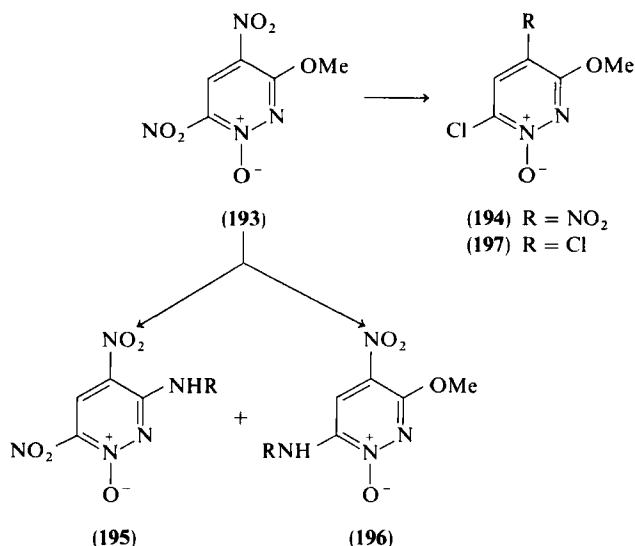
⁴³³ D. E. Klinge and H. C. Van der Plas, *Rec. Trav. Chim. Pays-Bas* **94**, 233 (1975).

⁴³⁴ D. E. Klinge, H. C. Van der Plas, and A. Van Veldhuizen, *Rec. Trav. Chim. Pays-Bas* **95**, 21 (1976).

⁴³⁵ T. Sakamoto and H. C. Van der Plas, *J. Heterocycl. Chem.* **14**, 789 (1977).

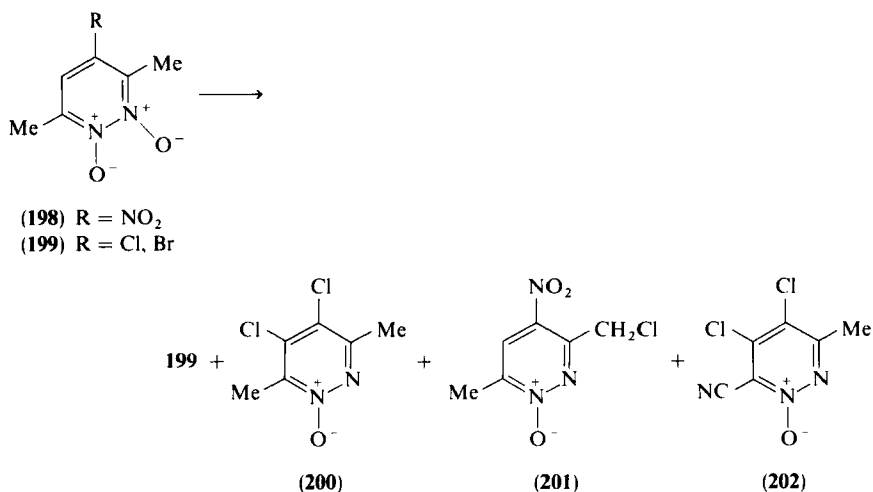
⁴³⁶ T. Novinson, R. K. Robins, and D. E. O'Brien, *J. Heterocycl. Chem.* **10**, 835 (1973).

⁴³⁷ M. Yanai, T. Kinoshita, S. Takeda, and H. Sedaki, *Chem. Pharm. Bull.* **20**, 166 (1972).



SCHEME 8

199 also three other compounds (**200**, **201**, and **202**) were isolated in low yield (Scheme 9).⁴³⁸ The cyano compound (**202**) must arise from nitrous acid formed from the NO₂ group. With phosphorus oxychloride, halogen introduction is accompanied by complete deoxygenation.⁴³⁹



SCHEME 9

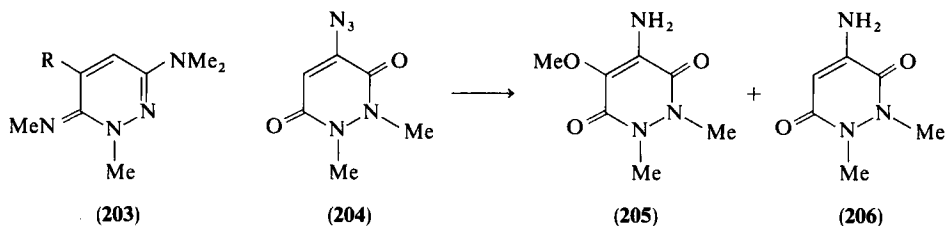
⁴³⁸ S. Sueyoshi and I. Suzuki, *Chem. Pharm. Bull.* **23**, 2767 (1975).

⁴³⁹ S. Sueyoshi and I. Suzuki, *Yakugaku Zasshi* **95**, 1327 (1975) [*CA* **84**, 74204 (1976)].

Kinetic studies of the reactions with sodium methoxide revealed that the 3- and 4-methylsulfinyl pyridazines were practically as reactive as the corresponding methylsulfonyl compounds, but that the methylthio compounds were less reactive by 10^4 to 10^5 . An anomalous reaction was observed with 4-methylsulfinylpyridazine and sodium methoxide to give, besides the 4-methoxy compound, also the 4-methylthio derivative in 6% yield.⁴⁴⁰ Replacement of the methylsulfinyl group with other nucleophiles has been investigated.⁴⁴¹

Some modifications of amino and hydrazino groups were also performed. An amino group can be replaced in the reaction with amines, although in low yield.⁴⁴² To the few known pyridazinonimines some new compounds have been added. The imines (**203**) are prepared from the corresponding pyridazinium salts and sodium hydride.⁴⁴³ Hydrazinopyridazines upon nitrosation are transformed into azido- or tetrazolopyridazines. The reaction can be complicated by aza-transfer reactions with a heterocyclic diazo compound. For example, 3-chloro-6-hydrazinopyridazine, when treated with 3-diazoindazole in methanol, is transformed into a mixture of 3-amino-6-chloropyridazine, 6-chloro-, and 6-methoxytetrazolopyridazine, indazole and its 3-amino and 3-azido derivatives.⁴⁴⁴

There are new investigations of azido-tetrazolo isomerization in the pyridazine series. Kinetic studies on the formation of iminophosphoranes have been published^{445,446} and the thermal behavior of azidopyridazinones were investigated. For example, compound **204** when heated in methanol at 130° is transformed into a mixture of **205** and **206**.⁴⁴⁶



An efficient new synthesis of pyridazine-4-carboxylic acid from 4-methyl-3,6-dichloropyridazine is described.⁴⁴⁷ The acid can be conveniently con-

⁴⁴⁰ G. B. Barlin and W. V. Brown, *J. Chem. Soc. B*, 1435 (1968).

⁴⁴¹ G. B. Barlin and W. V. Brown, *J. Chem. Soc. C*, 921 (1969).

⁴⁴² H. G. O. Becker, H. Böttcher, and J. Koch, *J. Prakt. Chem.* **311**, 286 (1969).

⁴⁴³ E. Kelstrup, *Acta Chem. Scand.* **23**, 2534 (1969).

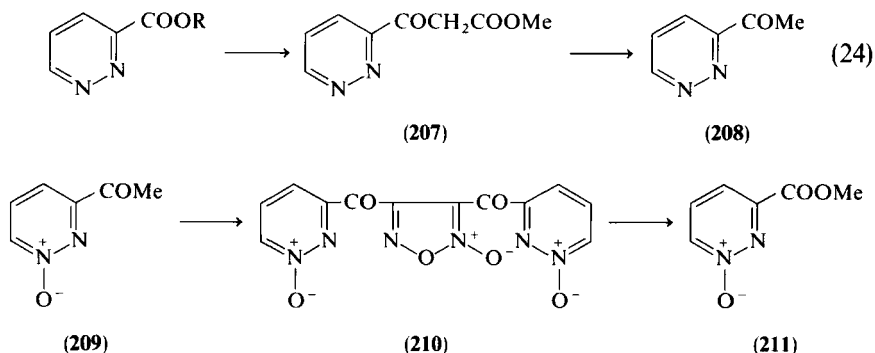
⁴⁴⁴ B. Stanovnik, M. Tišler, S. Polanc, V. Kovačič-Bratina, and B. Špicer-Smolnikar, *Tetrahedron Lett.*, 3193 (1976).

⁴⁴⁵ T. Sasaki, K. Kanematsu, and M. Murata, *Tetrahedron* **28**, 2383 (1972).

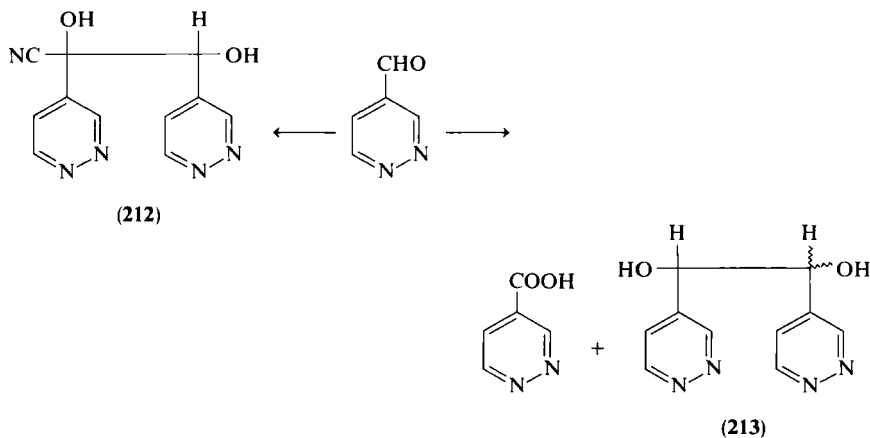
⁴⁴⁶ T. Sasaki, K. Kanematsu, and M. Murata, *Tetrahedron* **29**, 529 (1973).

⁴⁴⁷ G. Heinisch, *Monatsh. Chem.* **104**, 953 (1973).

verted into 4-acetylpyridazine. A better synthesis of 3-acetylpyridazine involves a Claisen condensation between the corresponding pyridazine ester and methyl acetate, and the product **207** is hydrolyzed and decarboxylated to **208** [Eq. (24)].^{448,449} The N-oxide (**209**) (or its ethylene ketal) is transformed by nitric acid into the furoxan derivative **210** which gives with hot methanol the ester **211**.⁴⁴⁸ Pyridazine-4- or 3-carbaldehydes do not form



the corresponding cyanhydrins, and instead the α -hydroxycyanhydrin **212** is obtained.^{450,451} Under the conditions of the benzoin reaction the aldehyde



SCHEME 10

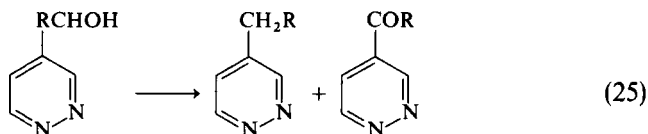
⁴⁴⁸ T. Nakagome and R. N. Castle, *J. Heterocycl. Chem.* **5**, 379 (1968).

⁴⁴⁹ G. P. Sokolov and S. Giller, *Khim. Geterotsikl. Soedin.*, 556 (1967).

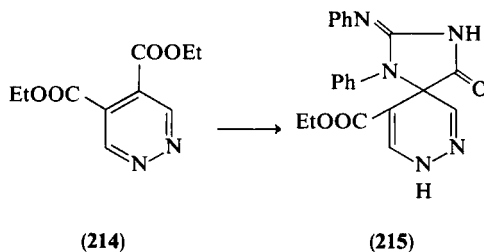
⁴⁵⁰ G. Heinisch, E. Luszczak, and M. Pailer, *Monatsh. Chem.* **104**, 1372 (1973).

⁴⁵¹ G. Heinisch, E. Luszczak, and A. Mayrhofer, *Monatsh. Chem.* **107**, 799 (1976).

is converted into a mixture of the 4-carboxylic acid and two stereoisomeric diols **213**,⁴⁵¹ probably by a crossed Cannizzaro reaction of the intermediate benzoinlike product and unchanged aldehyde (Scheme 10). Pyridazinyl-4-carbinols upon heating at 120° are transformed into a mixture of the corresponding 4-alkyl- and 4-acylpyridazines (Eq. 25).⁴⁵²



The rates of alkaline hydrolysis of methyl pyridazine-3- and -4-carboxylate were correlated with those of pyridinecarboxylates and benzoates.⁴⁵³ Diethyl pyridazine-4,5-dicarboxylate (**214**) reacts with 1,3-diphenylguanidine in the presence of sodium hydride to give the spiro compounds **215**, the structure of which was determined by X-ray analysis.^{454,455} Related spiro compounds were obtained from the above ester and esters of glutaric or acetonedicarboxylic acids.^{454,455} 5-Aminopyridazine-4-carboxylic acid is simply synthesized from the 5-carboxamido analog by Hofmann rearrangement.⁴⁵⁶



Functional groups or side chains of pyridazines have been used in the formation of new heterocyclic rings. Hydrazinopyridazines, when condensed with 1,3-dicarbonyl compounds give *N*-pyridazinylpyrazoles.^{457,458} Azido-pyridazines and acetylenes give triazolylpyridazines on which various re-

⁴⁵² G. Heinisch, E. Luszczak, and M. Pailer, *Monatsh. Chem.* **105**, 763 (1974).

⁴⁵³ L. W. Deady, D. J. Foskey, and R. A. Shanks, *J. Chem. Soc. B*, 1962 (1971).

⁴⁵⁴ G. Adembri, S. Chimichi, F. De Sio, R. Nesi, and M. Scotton, *Chim. Ind. (Milan)* **58**, 217 (1976).

⁴⁵⁵ G. Adembri, S. Chimichi, R. Nesi, and M. Scotton, *J.C.S. Perkin I*, 1020 (1977).

⁴⁵⁶ S. Chimichi and R. Nesi, *J. Heterocycl. Chem.* **14**, 1099 (1977).

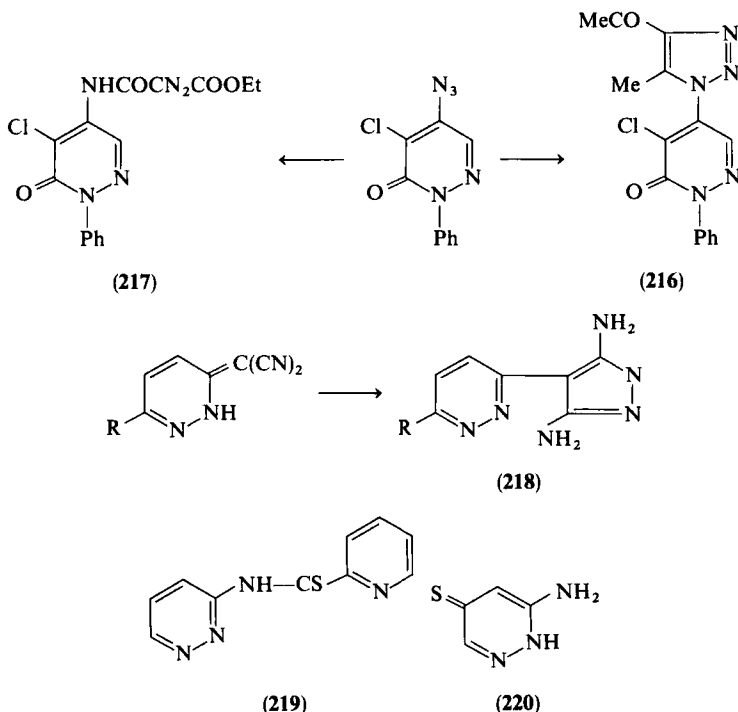
⁴⁵⁷ G. Westphal and P. Henklein, *Z. Chem.* **9**, 305 (1969).

⁴⁵⁸ H. Jahine, A. Sayed, H. A. Zaher, and O. Sherif, *Indian J. Chem.* **15B**, 250 (1977).

actions were performed.⁴⁵⁹⁻⁴⁶⁷ The azides also react with the enol form of a 1,3-dicarbonyl compound to give cycloadducts (**216**) or, after ring opening, compounds **217** and the corresponding aminopyridazine as the main product.⁴⁶⁸⁻⁴⁷⁰ The synthesis of pyridazinyl isoxazoles is described,⁴⁷¹ and 3-cyanopyridazine reacts with dicyandiamide to give a pyridazinyl-1,3,5-triazine.⁴⁷² Cyano-substituted 3-methylene derivatives of pyridazine react with hydrazine hydrate to give pyrazolyl derivatives (**218**).⁴⁷³

Heteroaromatic amines react with alkylpyridines in the presence of sulfur to give the corresponding thioamides. For example, from 3-aminopyridazine, with 2-methylpyridine and sulfur, compound **219** is obtained. When, however, the 2-methylpyridine (or diethyl malonate) was used in catalytic amount, 3-aminopyridazine-5(2*H*)-thione (**220**) was obtained at 160°-170°C.⁴⁷⁴ Pyridazine-3-thiones react with α -halocarbonyl compounds to give the corresponding keto-sulfides, which can be further cyclized.⁴⁷⁵

- ⁴⁵⁹ E. Gudriniece and V. Urbans, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, 82 (1971) [CA 74, 125600 (1971)].
- ⁴⁶⁰ A. Karklīnya and E. Yu. Gudriniece, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, 579 (1969) [CA 72, 55344 (1970)].
- ⁴⁶¹ A. H. Karklīnya and E. Yu. Gudriniece, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, 606 (1969) [CA 72, 66882 (1970)].
- ⁴⁶² A. H. Karklīnya and E. Yu. Gudriniece, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, 449 (1970) [CA 74, 13083 (1971)].
- ⁴⁶³ V. V. Solov'eva and E. Gudriniece, *Latv. PSR Zinat. Akad. Vestis, Khim. Ser.*, 572 (1972) [CA 78, 16120 (1973)].
- ⁴⁶⁴ V. Urbans and E. Gudriniece, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, 107 (1972) [CA 76, 153690 (1972)].
- ⁴⁶⁵ V. Urbans, E. Gudriniece, and T. V. Kotenko, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, 353 (1972) [CA 77, 88450 (1972)].
- ⁴⁶⁶ V. Urbans, E. Gudriniece, and L. A. Khoroshanskaya, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, 712 (1972) [CA 78, 72035 (1973)].
- ⁴⁶⁷ V. Urbans, E. Gudriniece, and L. A. Khoroshanskaya, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, 715 (1972) [CA 78, 72036 (1973)].
- ⁴⁶⁸ E. Gudriniece and V. V. Solov'eva, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, 378 (1970) [CA 73, 77172 (1970)].
- ⁴⁶⁹ E. Gudriniece and V. V. Solov'eva, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, 81 (1972) [CA 76, 153691 (1972)].
- ⁴⁷⁰ V. V. Solov'eva and E. Yu. Gudriniece, *Khim. Geterotsikl. Soedin.*, 256 (1973).
- ⁴⁷¹ L. S. Crawley and W. J. Fanshawe, *J. Heterocycl. Chem.* **14**, 531 (1977).
- ⁴⁷² F. H. Case, *J. Heterocycl. Chem.* **5**, 223 (1968).
- ⁴⁷³ M. Drobníč-Košorok, K. Jernejc-Pfundner, J. Peternel, B. Stanovnik, and M. Tišler, *J. Heterocycl. Chem.* **13**, 1279 (1976).
- ⁴⁷⁴ L. Kramberger, P. Lorenčák, S. Polanc, B. Verček, B. Stanovnik, M. Tišler, and F. Považanec, *J. Heterocycl. Chem.* **12**, 337 (1975).
- ⁴⁷⁵ K. Arakawa, T. Miyasaka, and K. Satoh, *Chem. Pharm. Bull.* **25**, 299 (1977).



In the free bases of methylpyridazines the 4-methyl hydrogens are more easily replaced than the 3-methyl ones in base-catalyzed hydrogen exchange.⁴⁷⁶ However, in the 1-oxide series the following order of reactivity was established: 6-Me > 5-Me > 4-Me \approx 3-Me. This order is similar to that observed for the base-catalyzed hydrogen exchange of the ring hydrogens of pyridazine and its *N*-oxide. Methylpyridazines can be brominated at the methyl group with *N*-bromosuccinimide in the presence of dibenzoyl peroxide to give the mono- or dibromo compounds.⁴⁷⁷ Nucleophilic displacement of the halogen in a chloromethyl group proceeds normally.⁴⁷⁸

From decarboxylation rates of pyridazinylacetic acids, it is concluded that decarboxylation takes place preferentially by the zwitterionic mechanism.^{479,480} Pyridazine catalyzes ester hydrolysis.⁴⁸¹

⁴⁷⁶ Y. Kawazoe, Y. Yoshioka, M. Yamada, and H. Igeta, *Chem. Pharm. Bull.* **15**, 2000 (1967).

⁴⁷⁷ G. Leclerc and C. G. Wermuth, *C.R. Acad. Sci., Ser. C* **267**, 1242 (1968).

⁴⁷⁸ K. Yu. Novickii, N. K. Sadovaya, E. F. Kasyanova, and L. K. Semina, *Khim. Geterotsikl. Soedin.*, 412 (1970).

⁴⁷⁹ R. B. Button and P. J. Taylor, *J.C.S. Perkin II*, 557 (1973).

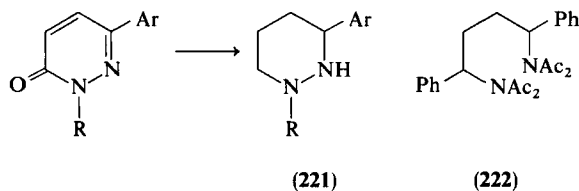
⁴⁸⁰ P. J. Taylor, *J.C.S. Perkin II*, 1077 (1972).

⁴⁸¹ J. A. Zoltewicz and H. L. Jacobson, *Tetrahedron Lett.*, 189 (1972).

Pyridazine glycosides have been phosphorylated, and the synthesis of some 5'-diphosphates or (3' → 5')diribonucleoside phosphates is described.^{482,483}

D. OXIDATIONS AND REDUCTIONS

The majority of known 1,4- and 1,6-dihydropyridazines are highly substituted or have strong electron-withdrawing groups on the pyridazine ring. Simple 1,6-dihydropyridazines have now been prepared from 1-methylpyridazinium salts and sodium borohydride.⁴⁸⁴ 1,4,5,6-Tetrahydropyridazines may be also obtained as by-products. These simple dihydropyridazines gradually decompose in the air at room temperature. If the reduction is performed in the presence of methyl chloroformate the stable *N*-methoxycarbonyl-1,6-dihydro compounds were obtained, accompanied with a small amount of the 1,4-dihydro isomers.⁴⁸⁴ A general mechanism for lithium aluminum hydride reduction of 3-pyrazolin-5-ones has been extended to pyridazin-3-ones.⁴⁸⁵ Reduction of a substituted 4,5-dihydropyridazine-3(2*H*)-one with lithium aluminum hydride gives the hexahydro compound (221),⁴⁸⁶ and similarly tetrahydropyridazine-3,6-diones give hexahydropyridazines.⁴⁸⁷



Study of the reduction of 2,3,4,5-tetrahydropyridazine-3-ones, which can be regarded as cyclic acylhydrazines, with lithium aluminum hydride revealed that, in proportions varying with conditions, 1,4,5,6-tetrahydropyridazines, hexahydropyridazines, and/or 1,4-dihydropyridazines are formed.⁴⁸⁸

Although 3,6-diphenyl-4,5-dihydropyridazine has been isolated and is reasonably stable,⁶⁰ related 4,5-dihydro analogs readily dimerize or trim-

⁴⁸² H. Pischel and A. Holy, *Collect. Czech. Chem. Commun.* **33**, 2066 (1968).

⁴⁸³ H. Pischel and A. Holy, *Collect. Czech. Chem. Commun.* **34**, 89 (1969).

⁴⁸⁴ C. Kaneko, T. Tsuchiya, and H. Igeta, *Chem. Pharm. Bull.* **22**, 2894 (1974).

⁴⁸⁵ J. Elguero, R. Jacquier, and D. Tizane, *Tetrahedron* **27**, 133 (1971).

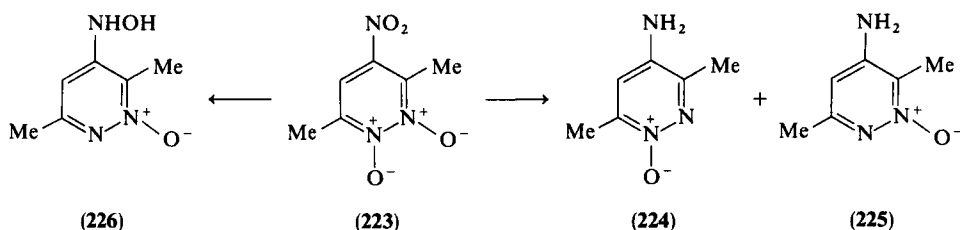
⁴⁸⁶ P. Aeberli and W. J. Houlihan, *J. Org. Chem.* **34**, 2720 (1969).

⁴⁸⁷ M. J. Kornet and H. S. I. Tan, *J. Pharm. Sci.* **61**, 1781 (1972).

⁴⁸⁸ J. L. Aubagnac, J. Elguero, R. Jacquier, and R. Robert, *Bull. Soc. Chim. Fr.*, 2859 (1972).

erize.^{489,490} Electroreduction of pyridazines in the presence of acetic anhydride gives the acylated open-chain diamines (cf. **117** → **222**).⁴⁹¹ In aqueous solution a 1,2-dihydropyridazine is formed, which decomposes to nitrogen and an unsaturated hydrazino-aldehyde that polymerizes.⁴⁹² Allylic bromination of 1,2-dicarbomethoxy-1,2,3,6-tetrahydropyridazine followed by dehydrobromination gives 1,2-dicarbomethoxy-1,2-dihydropyridazine.^{493,494} Catalytic hydrogenation gives the hexahydro compound.⁴⁹⁵

Pyridazine 1,2-dioxides can be reduced with hydrogen in the presence of palladized charcoal to monoxides.^{294,438} For example, the dioxide **223** gives a mixture of the isomeric monoxides **224** and **225**, but with three moles of hydrogen compound **226** is formed.⁴³⁸ Pyridazine-3(2*H*)-one was reduced over platinum to 1,4,5,6-tetrahydropyridazine-3(2*H*)-one.⁴⁹⁶



Polarographic reduction of pyridazines and pyridazine 1,2-dioxide has been studied.^{294,497-499} The polarographic behavior of pyridazine is typical of an overall two-electron reduction process.⁵⁰⁰ In alkaline solution it is reduced polarographically to 1,4-dihydropyridazine, but in acid solutions this compound gives an open-chain aminoimine.⁴⁹⁹

A reinvestigation of the reduction of diethyl pyridazine-3,4- or -4,5-dicarboxylate with lithium aluminum hydride under controlled conditions

⁴⁸⁹ B. K. Bandlish, J. N. Brown, J. W. Timberlake, and L. M. Trefonas, *J. Org. Chem.* **38**, 1102 (1973).

⁴⁹⁰ P. De Mayo, J. B. Stothers, and M. C. Usselman, *Can. J. Chem.* **50**, 612 (1972).

⁴⁹¹ H. Lund and J. Simonet, *C.R. Acad. Sci., Ser. C* **277**, 1387 (1973).

⁴⁹² L. N. Klatt and R. L. Rouseff, *J. Electroanal. Chem. Interfacial Electrochem.* **41**, 411 (1973).

⁴⁹³ L. J. Altman, M. F. Semmelhack, R. B. Hornby, and J. C. Vederas, *Chem. Commun.*, 686 (1968).

⁴⁹⁴ L. J. Altman, M. F. Semmelhack, R. B. Hornby, and J. C. Vederas, *Org. Prep. Proced. Int.* **7**, 35 (1975).

⁴⁹⁵ Yu. S. Shabarov and L. D. Sychkova, *Zh. Obshch. Khim.* **42**, 2058 (1972).

⁴⁹⁶ E. Testa and L. Fontanella, *Farmaco, Ed. Sci.* **26**, 950 (1971).

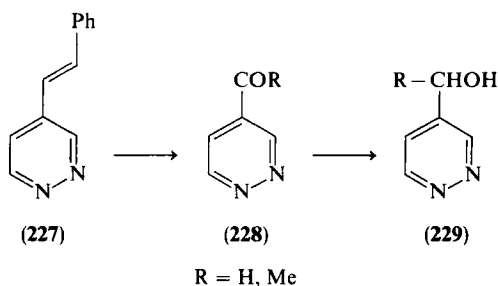
⁴⁹⁷ T. V. Glezer, J. P. Stradins, I. K. Tutane, L. Ya. Avota, and S. A. Giller, *Zh. Obshch. Khim.* **43**, 1150 (1973).

⁴⁹⁸ V. T. Glezer, Ya. P. Stradins, and L. Ya. Avota, *Khim. Geterotsikl. Soedin.*, 668 (1977).

⁴⁹⁹ S. Millefiori, *Ann. Chim. (Rome)* **59**, 15 (1969).

⁵⁰⁰ J. E. O'Reilly and P. J. Elving, *J. Am. Chem. Soc.* **94**, 7941 (1972).

allowed either the monoformyl or the diformyl compound to be obtained.⁵⁰¹ 4-Acetylpyridazine and pyridazine-4-carbaldehyde are reduced with sodium borohydride to the corresponding carbinols (**299**: R = H or Me).⁵⁰² Pyridazine-4-carbaldehyde (**228**: R = H) is prepared by oxidation of 4-styrylpyridazine (**227**), obtained by condensation of 4-methylpyridazine with benzaldehyde.⁴⁵⁰ A similar procedure can be applied to prepare the 3-aldehyde, which can be obtained also from the corresponding carbinol by oxidation with manganese dioxide.⁵⁰³ With sodium in liquid ammonia under Birch reduction conditions halopyridazines are dehalogenated.⁵⁰⁴



Oxidation of perhydropyridazines to 2,3,4,5-⁵⁰⁵ or 3,4,5,6-tetrahydropyridazines is reported.⁵⁰⁶ 3-(*o*-, *m*-, or *p*-Hydroxyphenyl)-1,4,5,6-tetrahydropyridazines are aromatized over platinum at elevated temperature, and to a minor extent nitrogen is eliminated to give cyclobutane derivatives.⁵⁰⁷

3-Cyanomethylenepyridazines (**230**), prepared either from halopyridazines or pyridazine *N*-oxides and malononitrile or ethyl cyanoacetate, are oxidized by 75% hydrogen peroxide in alkali to the 3-carboxylic acids (**231**).⁵⁰⁸ Oxidation of tetrazolo[(1,5-*b*)]pyridazine with concentrated hydrogen peroxide proceeds with simultaneous ring opening to give 3-azidopyridazine 1-oxide in low yield.⁵⁰⁹ Oxidation of mixed azinyl pyridazinyl sulfides involves *S*- or *N*-oxidation, but the predominant process is cleavage of the sulfide bond.⁵¹⁰ Radicals are obtained if maleic hydrazide analogs are

⁵⁰¹ A. Turck, G. Queguiner, and P. Pastour, *C.R. Acad. Sci., Ser. C* **277**, 33 (1973).

⁵⁰² G. Heinisch, *Monatsh. Chem.* **104**, 1354 (1973).

⁵⁰³ G. Heinisch and A. Mayrhofer, *Monatsh. Chem.* **108**, 213 (1977).

⁵⁰⁴ J. de Lannoy, A. Gysen, and R. Nasielski-Hinkens, *Bull. Soc. Chim. Belg.* **79**, 329 (1970).

⁵⁰⁵ K. Heyns and H. Buchholz, *Chem. Ber.* **109**, 3707 (1976).

⁵⁰⁶ T. R. Lynch, F. N. MacLachlan, and Y. K. Siu, *Can. J. Chem.* **49**, 1598 (1971).

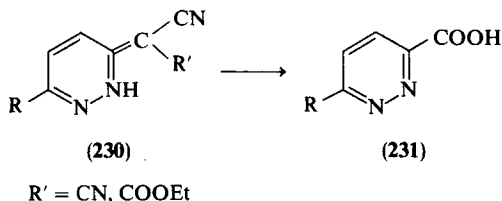
⁵⁰⁷ Yu. S. Shabarov, L. D. Sychkova, T. V. Leonova, and R. Ya. Levina, *Khim. Geterotsikl. Soedin.*, 657 (1970).

⁵⁰⁸ A. Pollak, B. Stanovnik, M. Tišler, and J. Venetič-Fortuna, *Monatsh. Chem.* **106**, 473 (1975).

⁵⁰⁹ B. Stanovnik, M. Tišler, M. Ceglar, and V. Bah, *J. Org. Chem.* **35**, 1138 (1970).

⁵¹⁰ A. Petrič, B. Stanovnik, and M. Tišler, *Chimia* **29**, 466 (1975).

treated with lead dioxide.⁵¹¹ Enzymic oxidations of pyridazines have been reported.⁵¹²



E. RING OPENING

As part of a study on 1,4-diradicals, various 3,4,5,6-tetrahydropyridazines were decomposed thermally⁵¹³⁻⁵¹⁸ to olefins and cyclobutane derivatives (see also Section III,G). The activation parameters were measured.^{519,520} The stereochemical paths of thermal and photochemical nitrogen extrusion from 3,4,5,6-tetrahydropyridazines have been reexamined and rationalized.⁵²¹ Kinetic measurements of the decomposition of 3,6-dimethyl-3,6-dicyano-3,4,5,6-tetrahydropyridazine have been made.⁵²² Pyridazines with specific functional group orientation can be used as starting material for the preparation of various dienes (Scheme 11). For example, compound **232** is quantitatively transformed into *trans,trans*-2,4-hexadiene (**233**), whereas the *trans* isomer **234** affords exclusively the *cis-trans* product (**235**).^{523,524} 1,2-Dimethyl-1,2,3,6-tetrahydropyridazine is thermally decomposed to give mainly *trans*-azomethane, with about 10% of the *cis*-isomer.⁵²⁵

⁵¹¹ W. H. Pirkle and P. L. Gravel, *J. Org Chem.* **42**, 1367 (1977).

⁵¹² S. Haug, J. Eberspaecher, and F. Lingens, *Biochem. Biophys. Res. Commun.* **54**, 760 (1973).

⁵¹³ P. B. Dervan and T. Ueyhara, *J. Am. Chem. Soc.* **98**, 1262 (1976).

⁵¹⁴ P. B. Dervan and T. Uyehara, *J. Am. Chem. Soc.*, **98**, 2003 (1976).

⁵¹⁵ K. R. Kopecky and S. Evani, *Can. J. Chem.*, **47**, 4041 (1969).

⁵¹⁶ K. R. Kopecky and J. Soler, *Can. J. Chem.*, **52**, 2111 (1974).

⁵¹⁷ T. J. Levek and E. F. Kiefer, *J. Am. Chem. Soc.*, **98**, 1875 (1976).

⁵¹⁸ R. C. Neuman and E. W. Ertley, *Tetrahedron Lett.*, 1225 (1972).

⁵¹⁹ P. S. Engel and D. J. Bishop, *J. Am. Chem. Soc.* **97**, 6754 (1975).

⁵²⁰ P. S. Engel, *J. Am. Chem. Soc.* **98**, 1972 (1976).

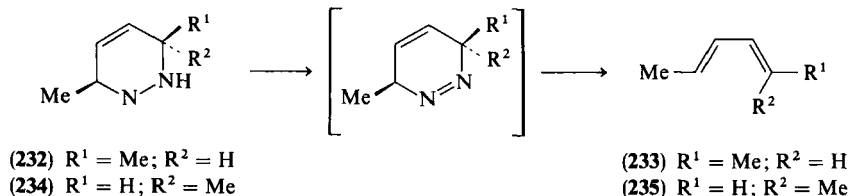
⁵²¹ S. Inagaki and K. Fukui, *Bull. Chem. Soc. Jpn.* **45**, 824 (1972).

⁵²² D. Lim, *Collect. Czech. Chem. Commun.*, **33**, 1122 (1968).

⁵²³ J. A. Berson and S. S. Olin, *J. Am. Chem. Soc.*, **91**, 777 (1969).

⁵²⁴ J. A. Berson, S. S. Olin, E. W. Petrillo, and P. Bickart, *Tetrahedron* **30**, 1639 (1974).

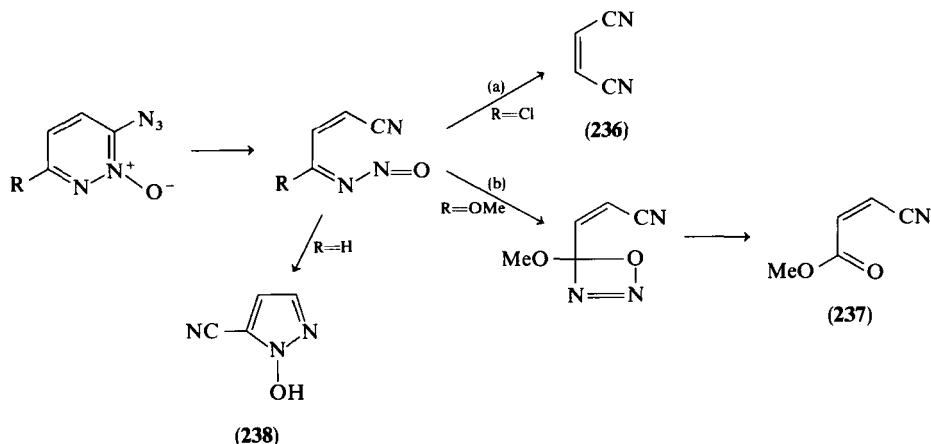
⁵²⁵ S. F. Nelsen, *J. Am. Chem. Soc.* **96**, 5669 (1974).



SCHEME 11

Thermal fragmentation of maleic hydrazide in the range of $450^\circ\text{--}800^\circ\text{C}$ proceeds by two pathways: (a) (2+2+2)-cycloreversion to give acetylene and isocyanic acid as primary products, and (b) a retro-Diels-Alder reaction to give initially diimide and a bisketene.⁵²⁶

Thermolysis of 6-substituted 3-azidopyridazine 2-oxides gives maleonitrile (**236**) or *cis*- β -cyanoacrylate (**237**), but the parent compound gives also traces of a pyrazole (**238**)⁵²⁷ (Scheme 12).



SCHEME 12

Products of γ -radiolysis of pyridazine are acetylene, nitrogen, hydrogen, and a polymer.⁵²⁸

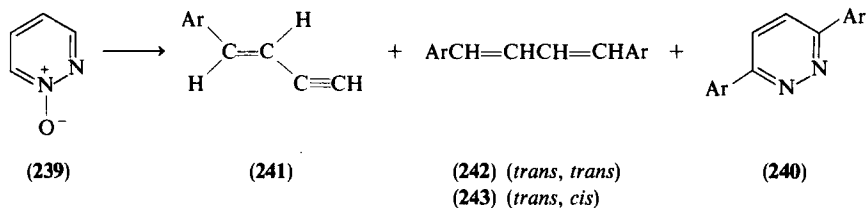
There are several examples of pyridazine ring opening under the action of nucleophiles. Pyridazine *N*-oxide and its methyl analogs react with Grignard reagents or phenyllithium to give the vinylacetylene **241**, the

⁵²⁶ S. C. Clough, J. C. Kang, W. R. Johnson, and T. S. Osdene, *Chem. Ind. (London)*, 323 (1973).

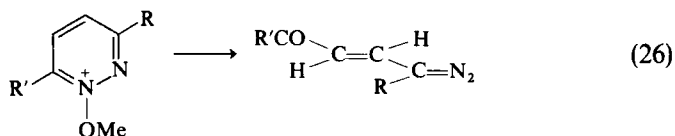
⁵²⁷ R. A. Abramovitch and I. Shinkai, *Chem. Commun.*, 703 (1975).

⁵²⁸ F. Lahmani and N. Ivanoff, *Radiat. Chem., Proc. Tihany Symp., 2nd*, 327 (1966) [*CA* **68**, 77466 (1968)].

isomeric butadienes **242** and **243** and the arylated pyridazine (**240**).⁵²⁹⁻⁵³¹



The nucleophile attacks adjacent to the *N*-oxide group, and ring-opening, attack of Ph^- at the conjugated system, and elimination of nitrogen follow. Similar ring opening reactions occur when *N*-methoxypyridazinium or *N*-benzoyloxypyridazinium salts are treated with cyanide, hydroxide, or dicyanomethyl ions.^{532,533} From *N*-methoxypyridazinium salts and hydroxide ion vinyl diazomethanes are obtained in high yield as shown in Eq. (26).⁵³⁴ 1,1-Dialkyl-1,4,5,6-tetrahydropyridazinium iodides when treated with alkali give γ -dialkylaminobutyronitriles.⁵³⁵



F. ISOMERIZATIONS, REARRANGEMENTS, AND RING CONTRACTIONS

In the last decade new reactions have been elaborated in which pyridazines can be transformed into a variety of other heterocycles. Esters of pyridazine-carboxylic acids and 1-diethylaminopropyne undergo cycloaddition reactions with inverse electron demand.⁵³⁶⁻⁵³⁸ The orientation of the two reactants depends on the position of the carboxylate group in the pyridazine ring. For example, from methyl pyridazine-4-carboxylate the pyridine derivative **245** was formed via the adduct **244** and subsequent elimination

⁵²⁹ G. Okusa, M. Kumagai, and T. Itai, *Chem. Commun.*, 710 (1969).

⁵³⁰ G. Okusa, M. Kumagai, and T. Itai, *Chem. Pharm. Bull.* **17**, 2502 (1969).

⁵³¹ H. Igeta, T. Tsuchiya, and T. Nakai, *Tetrahedron Lett.*, 2667 (1969).

⁵³² H. Igeta, C. Kaneko, and T. Tsuchiya, *Chem. Pharm. Bull.* **23**, 2798 (1975).

⁵³³ C. Kaneko, T. Tsuchiya, and H. Igeta, *Tetrahedron Lett.*, 2347 (1973).

⁵³⁴ T. Tsuchiya, C. Kaneko, and H. Igeta, *Chem. Commun.*, 528 (1975).

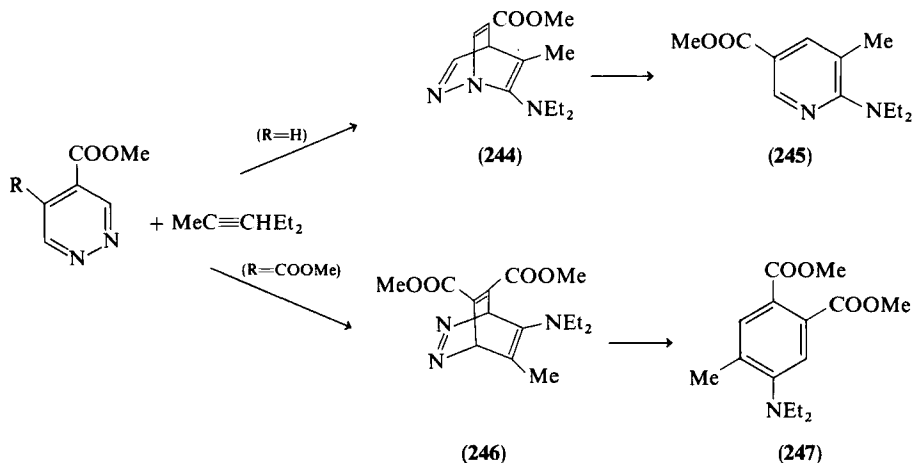
⁵³⁵ K. N. Zelenin and V. G. Kamerdinerov, *Khim. Geterotsikl. Soedin.*, 530 (1968).

⁵³⁶ H. Neunhoeffer and G. Werner, *Tetrahedron Lett.*, 1517 (1972).

⁵³⁷ H. Neunhoeffer and G. Werner, *Justus Liebigs Ann. Chem.*, 437 (1973).

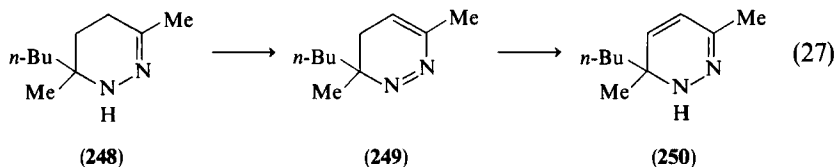
⁵³⁸ H. Neunhoeffer and G. Werner, *Justus Liebigs Ann. Chem.*, 1955 (1973).

of HCN. By contrast, dimethyl pyridazine-4,5-dicarboxylate is transformed into the benzene derivative **247** after nitrogen elimination from **246** (Scheme 13).^{536,537} A similar reaction with 1-methoxy-*N,N*-dimethylvinylamine also gives benzene derivatives.⁵³⁸



SCHEME 13

2,3-Dihydropyridazines are rearranged thermally or by a base into the 1,4-dihydro isomers.⁵⁴ The 5,6-dihydropyridazine derivative **249**, obtained after halogenation and dehydrohalogenation of the tetrahydro derivative **248**, is the first fully characterized representative of a 5,6-dihydropyridazine. Upon heating it undergoes a 1,5-sigmatropic hydrogen rearrangement to give the 1,6-dihydro derivative (**250**) [Eq. (27)].⁵³⁹

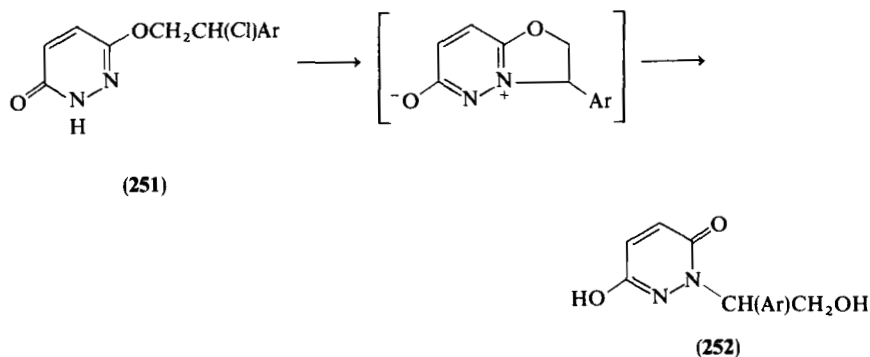
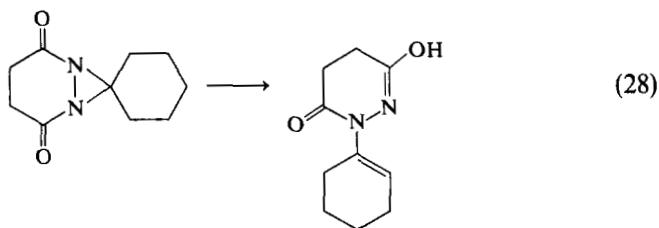


A diazirinopyridazine is thermally isomerized to the 1-substituted pyridazine as shown in Eq. (28).⁵⁴⁰ The chloro compound **251**, obtained by phenacylation of maleic hydrazide and subsequent reduction and chlorination, is rearranged in the presence of sodium hydroxide to **252**, probably via an oxazolinium intermediate.⁵⁴¹

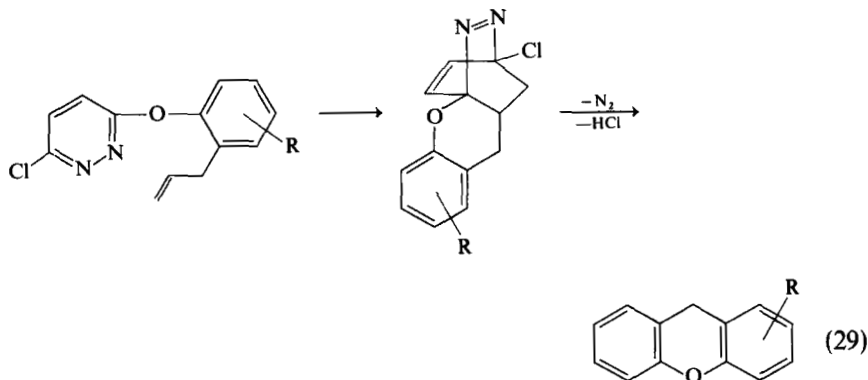
⁵³⁹ P. De Mayo and M. C. Usselman, *Can. J. Chem.* **51**, 1724 (1973).

⁵⁴⁰ H. W. Heine, R. Henrie, L. Heitz, and S. R. Kovvali, *J. Org. Chem.* **39**, 3187 (1974).

⁵⁴¹ R. Jaunin, *Chim. Ther.* **2**, 317 (1967).



An interesting reaction is the thermal conversion of allylphenoxypyridazines into xanthenes as shown in Eq. (29).^{542,543} The reaction involves an



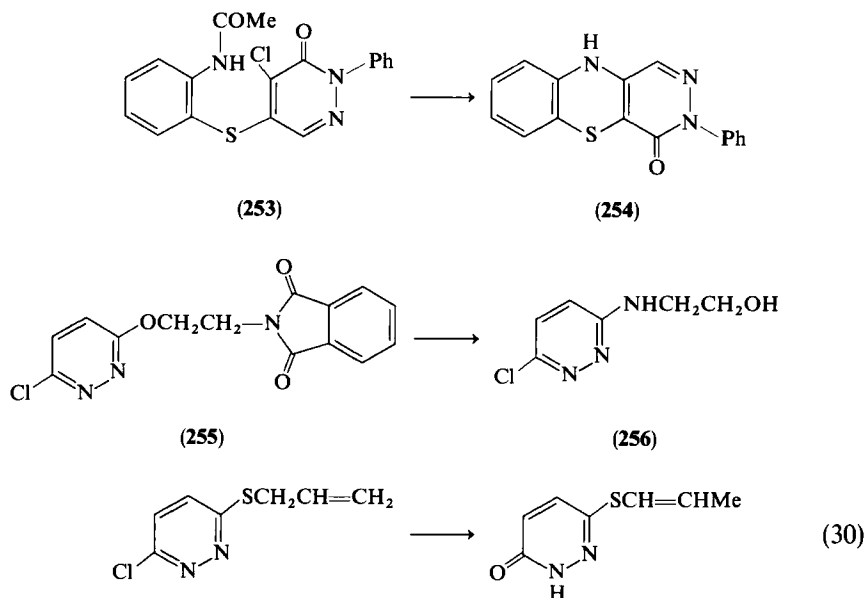
intramolecular cycloaddition to give a (4+2) cycloadduct followed by elimination of nitrogen and hydrogen chloride. If the allylic side chain is replaced with the 2-methylallyl group, the reaction stops at the dihydroxanthene stage.⁵⁴³ Such products are also obtained with pyridazines having

⁵⁴² T. Jojima, H. Takeshiba, and T. Konotsune, *Chem. Pharm. Bull.* **20**, 2191 (1972).

⁵⁴³ T. Jojima, H. Takeshiba, and T. Kinoto, *Chem. Pharm. Bull.* **24**, 1581 (1976).

instead of a chlorine atom a nonleaving group, such as alkyl or aryl, at position 3.⁵⁴⁴

Examples of Smiles rearrangements are known in the pyridazine series.^{402,545,546} The rearrangement occurs thermally or is base or less completely acid-catalyzed. Contrary to previous observations, alkaline treatment of **253** yields exclusively **254**.^{545,547} Smiles rearrangement is observed also when the phthalimido derivative **255** is treated with hydrazine to give the hydroxyethylamino compound **256**.⁵⁴⁸



3-Allylthio-6-chloropyridazine when heated with alkali does not undergo thio-Claisen rearrangement, but is isomerized to the 3-propenylthio derivative with concurrent hydrolysis of the halogen atom [Eq. (30)]⁵⁴⁹

Perfluoropyridazines and perfluoroalkyl analogs are thermally isomerized predominantly to perfluoropyrimidines (**258**), in contrast to their photochemical isomerization exclusively to perfluoropyrazines (e.g., **259**) (Section

⁵⁴⁴ T. Jojima, H. Takeshiba, and T. Kinoto, *Chem. Pharm. Bull.* **24**, 1588 (1976).

⁵⁴⁵ Y. Maki, M. Suzuki, O. Toyota, and M. Takaya, *Chem. Pharm. Bull.* **21**, 241 (1973).

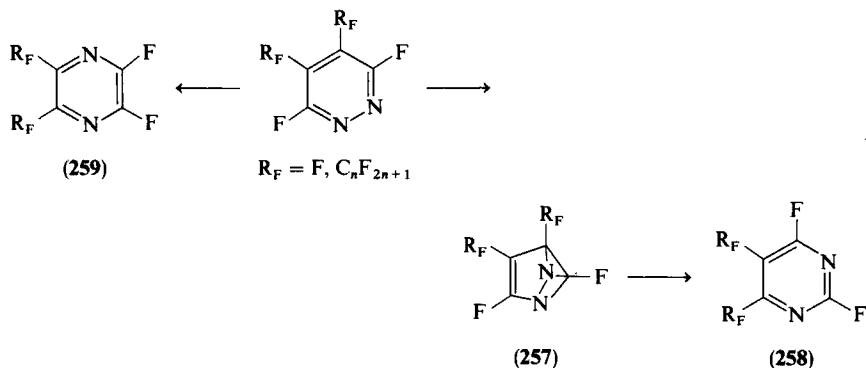
⁵⁴⁶ Y. Maki and M. Suzuki, *Yakugaku Zasshi* **93**, 171 (1973) [*CA* **78**, 136195 (1973)].

⁵⁴⁷ G. Scapini, F. Duro, and G. Pappalardo, *Ann. Chim. (Rome)* **58**, 718 (1968).

⁵⁴⁸ V. G. Ermolaeva, M. N. Shchukina, and N. F. Korolenok, *Khim. Geterotsikl. Soedin.*, 124 (1974).

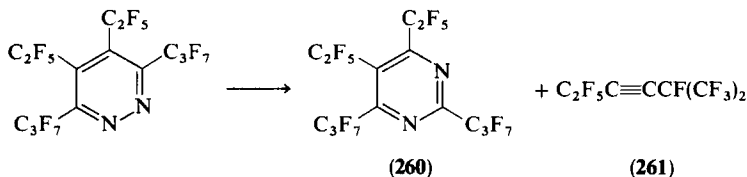
⁵⁴⁹ M. Kočevár, B. Stanovnik, and M. Tišler, *Croat. Chem. Acta* **45**, 457 (1973).

III,G) (Scheme 14).⁵⁵⁰⁻⁵⁵² Thermal isomerization is postulated to proceed



SCHEME 14

via a diazabenzovalene (**257**). Thus, pyrolysis of tetrafluoropyridazine at 815°C gives tetrafluoropyrimidine (46%) and a little tetrafluoropyrazine. These rearrangements have been explained by valence isomerization to intermediate diazabenzovalenes (cf. **257**). In some cases, as for example with perfluoro-4,5-diethylpyridazine, rearrangement leaves the relative position of pentafluoroethyl groups unchanged (as in **258**).^{551,553} On the other hand, pyrolysis of perfluorotetraphenylpyridazine and some perfluoroalkylaryl derivatives at about 700°C proceeds with elimination of nitrogen and formation of perfluorinated acetylenes.⁵⁵⁴ Perfluoro-4,5-diethyl-3,6-diisopropylpyridazine upon pyrolysis at 650°C undergoes both nitrogen elimi-



⁵⁵⁰ C. G. Allison, R. D. Chambers, J. A. Cheburkov, J. A. H. MacBride, and W. K. R. Musgrave, *Chem. Commun.*, 1200 (1969).

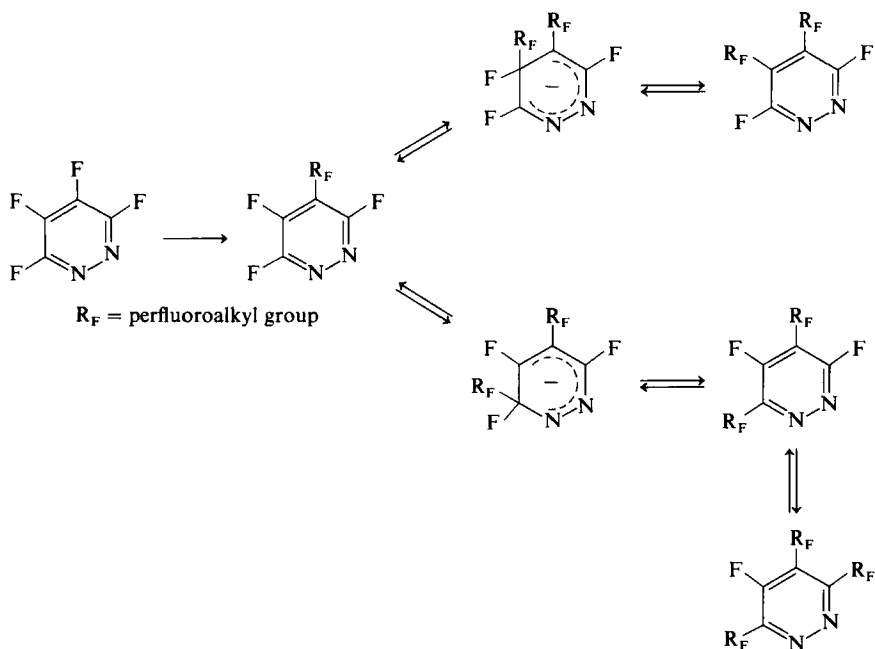
⁵⁵¹ R. D. Chambers, M. Clark, J. R. Maslakiewicz, W. K. R. Musgrave, and P. G. Urben, *J. C. S. Perkin I*, 1513 (1974).

⁵⁵² R. D. Chambers, J. A. H. MacBride, and W. K. R. Musgrave, *J. Chem. Soc. C*, 3384 (1971).

⁵⁵³ R. D. Chambers, M. Clark, J. R. Maslakiewicz, and W. K. R. Musgrave, *Tetrahedron Lett.*, 2405 (1973).

⁵⁵⁴ R. D. Chambers, M. Clark, J. A. H. MacBride, W. K. R. Musgrave, and K. C. Srivastava, *J.C.S. Perkin I*, 125 (1974).

nation and rearrangement, giving approximately equal amounts of **260** and **261**.⁵⁵¹ Several cases of fluoride-catalyzed rearrangements and disproportionations of perfluoroalkyl-substituted pyridazines have been observed^{407,555,556}; reversible addition of the corresponding perfluoroalkyl anion is invoked (Scheme 15).



SCHEME 15

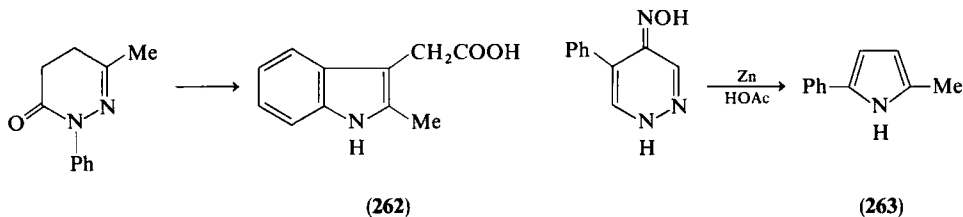
New examples of base- or acid-induced ring contraction of pyridazines include the formation of azoles. An investigation of the known cyclization of the phenylhydrazone of ethyl levulinate to pyridazinone revealed that in the presence of BF_3 -etherate the corresponding indole derivative (**262**) is obtained.⁵⁵⁷ The latter is formed also from the pyridazinone and ethanolic hydrogen chloride. 5-Phenylpyridazinone-4-oxime, when treated with zinc in acetic acid, is rearranged to the pyrrole **263**.⁵⁵⁸

⁵⁵⁵ R. D. Chambers, Yu. A. Cheburkov, J. A. H. MacBride, and W. K. R. Musgrave, *Chem. Commun.*, 1647 (1970).

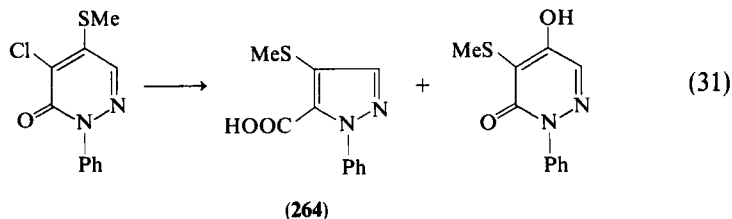
⁵⁵⁶ C. J. Drayton, W. T. Flowers, and R. N. Haszeldine, *Chem. Commun.*, 662 (1970).

⁵⁵⁷ J. Bagot, O. Siffert, and B. Millet, *Bull. Soc. Chim. Fr.*, 917 (1969).

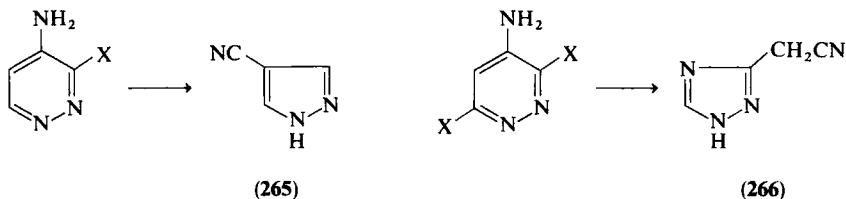
⁵⁵⁸ E. Aiello, *Atti Accad. Sci., Lett. Arti Palermo, Parte I* **27**, 465 (1966-1967) [*CA* **71**, 12919 (1969)].



The ring contraction of pyridazinones to pyrazoles has been further investigated.⁵⁵⁹⁻⁵⁶² 1-Phenyl-4,5-disubstituted pyridazin-6-ones are transformed with hot alkali into pyrazoles (264), accompanied sometimes by other substituted pyridazines. Unexpectedly, 1-phenyl-4-methylthio-5-chloro-pyridazin-6-one gave in addition to 264 also another pyridazine [Eq. (31)],⁵⁵⁹ which originates by the attack of the liberated methylthio anion on the starting compound.



In one preparation of 5-methylamino-4-nitro-1-phenylpyridazin-6-one from the corresponding 5-hydroxy compound and aqueous methylamine, an equal amount of 1-phenyl-3-nitropyrazole was obtained.⁵⁶³ 4-Amino-3-halopyridazines with excess of potassium amide in liquid ammonia are rearranged to 4-cyanopyrazole (265), whereas the 3,6-dihalo analog gives 3-cyanomethyl-1,2,4-triazole (266).⁵⁶⁴ The proposed mechanism involves



⁵⁵⁹ Y. Maki and M. Takaya, *Chem. Pharm. Bull.* **19**, 1635 (1971).

⁵⁶⁰ Y. Maki, G. P. Beardsley, and M. Takaya, *Tetrahedron Lett.*, 1507 (1971).

⁵⁶¹ Y. Maki and M. Takaya, *Chem. Pharm. Bull.* **20**, 747 (1972).

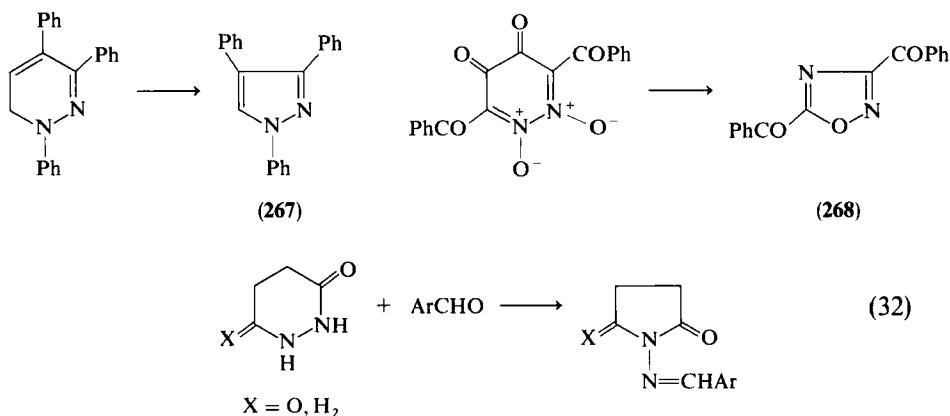
⁵⁶² Y. Maki, M. Suzuki, and M. Takaya, *Chem. Pharm. Bull.* **22**, 229 (1974).

⁵⁶³ G. S. Predvoditeleva, T. V. Kartseva, and M. N. Shchukina, *Khim. Farm. Zh.* **8**, 7 (1974).

⁵⁶⁴ D. E. Klinge, H. C. Van der Plas, G. Geurtsen, and A. Koudijs, *Rec. Trav. Chim. Pays-Bas* **93**, 236 (1974).

abstraction of hydrogen at the amino group (with a 4-methylamino compound no ring contraction occurs), ring opening, and cyclization. 1,3,4-Triphenyl-1,6-dihydropyridazine rearranges in dilute acid at 20°C with oxidative loss of C(6), to 1,3,4-triphenylpyrazole (**267**).⁵⁶⁵

A reinvestigation of the conversion of 3,6-dibenzoylpyridazine-4,5-dione 1,2-dioxide to a 1,2,4-oxadiazole (**268**) has confirmed the structures and elucidated the mechanism.⁵⁶⁶



Hexahydropyridazine-3-one and the 3,6-dione react with aromatic aldehydes, and the condensation is accompanied with rearrangement to a five-membered ring [Eq. (32)].⁵⁶⁷

G. PHOTOREACTIONS

Numerous photochemical transformations of pyridazines and their *N*-oxides have been reported by several groups. The lowest singlet-triplet transition observed for pyridazine in rigid-glass solution⁵⁶⁸ was later revised,⁵⁶⁹ and the intersystem crossing quantum yield was determined.⁵⁷⁰ Photolysis of pyridazine in the gas phase gives nitrogen and vinylacetylene as main products.⁵⁷¹

⁵⁶⁵ A. Padwa and L. Gehrlein, *J. Heterocycl. Chem.* **12**, 589 (1975).

⁵⁶⁶ C. W. Bird, *Tetrahedron Lett.*, 1703 (1976).

⁵⁶⁷ J. Gut, A. Novacek, and P. Fiedler, *Collect. Czech. Chem. Commun.* **33**, 2087 (1968).

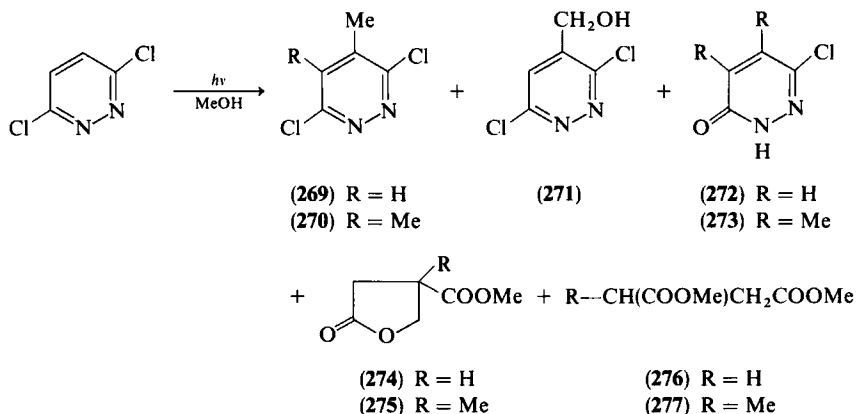
⁵⁶⁸ K. Yamamoto, T. Tekamura, and H. Baba, *Bull. Chem. Soc. Jpn.* **48**, 2599 (1975).

⁵⁶⁹ C. J. Harzaccoco, *Bull. Chem. Soc. Jpn.* **50**, 771 (1977).

⁵⁷⁰ T. Takemura, K. Yamamoto, I. Yamazaki, and H. Baba, *Bull. Chem. Soc. Jpn.* **45**, 1639 (1972).

⁵⁷¹ J. R. Fraser, L. H. Low, and N. A. Weir, *Can. J. Chem.* **53**, 1456 (1975).

3,6-Dichloropyridazine, when briefly irradiated in acidified methanol, gives the pyridazines **269**–**273** as main products (Scheme 16); prolonged irradiation gives compounds **274**–**277** as main products.⁵⁷² According to the proposed mechanism, **271** is transformed into **274** and **275** and further to **276** and **277**. Under similar reaction conditions other pyridazines also give γ -lactones and succinates.^{573,574} In the same reaction medium pyridazine is transformed upon irradiation into its 4-methyl and 4,5-dimethyl derivative.⁵⁷⁵ Other substituted pyridazines undergo photoinduced methylation in low yield.



SCHEME 16

Ring contraction occurs also on irradiation of pyridazine-3(2*H*)-ones to give a mixture of pyrrolines **278** and **279** (minor product).⁵⁷⁶ Similarly, 3-methyl-1-phenyl-hexahydropyridazine-6-one gives **280**.⁵⁷⁷ However, photolysis of 5-amino-4-chloro-2-phenylpyridazine-3(2*H*)-one, a selective herbicide, in sunlight gives a mixture of **281** and **282**, the last compound originating from **281**.⁵⁷⁸ The first photoisomerization of 3-hydroxypyridazinium betaines into pyrimidinones converts **283** into **284**; the mechanism proposed involves valence isomerization.⁵⁷⁹

⁵⁷² T. Tsuchiya, H. Arai, and H. Igeta, *Tetrahedron Lett.*, 3839 (1970).

⁵⁷³ T. Tsuchiya, H. Arai, and H. Igeta, *Chem. Pharm. Bull.* **19**, 1108 (1971).

⁵⁷⁴ T. Tsuchiya, H. Arai, H. Kawamura, and H. Igeta, *Chem. Pharm. Bull.* **20**, 269 (1972).

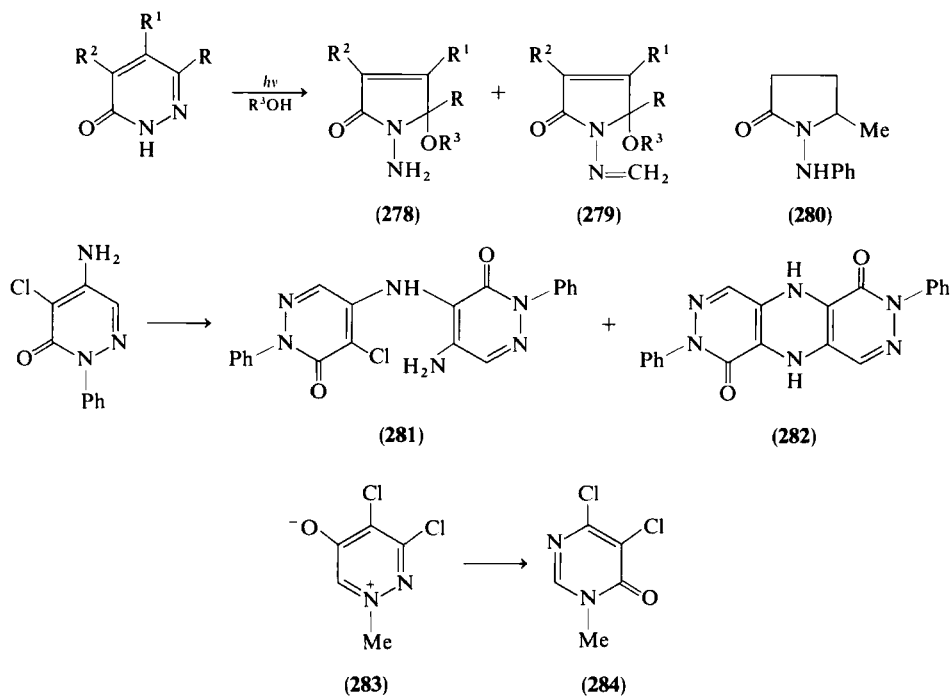
⁵⁷⁵ T. Tsuchiya, H. Arai, and H. Igeta, *Chem. Pharm. Bull.* **20**, 273 (1972).

⁵⁷⁶ T. Tsuchiya, M. Hasebe, H. Arai, and H. Igeta, *Chem. Pharm. Bull.* **22**, 2276 (1974).

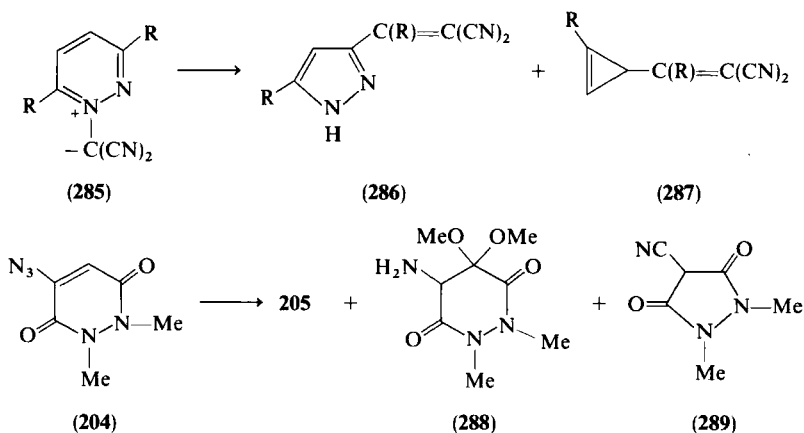
⁵⁷⁷ S. N. Ege, M. L. C. Carter, D. F. Ortwine, S. S. P. Chou, and J. F. Richman, *J.C.S. Perkin I*, 1252 (1977).

⁵⁷⁸ J. D. Rosen and M. Siewierski, *J. Agric. Food Chem.* **20**, 434 (1972).

⁵⁷⁹ Y. Maki, M. Suzuki, T. Furuta, T. Hiramitsu, and M. Kuzuya, *Tetrahedron Lett.*, 4107 (1974).



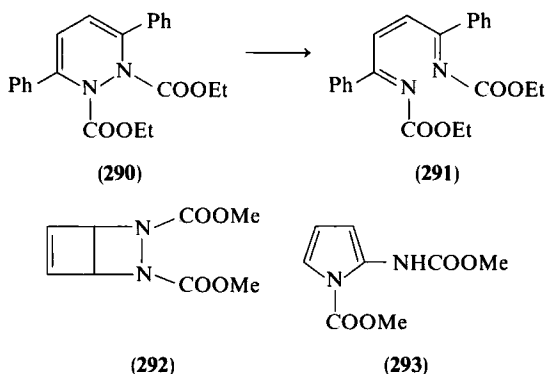
trans-Styrylpyridazines are photoisomerized into *cis*-isomers, which could be separated from the photostationary equilibrium mixture.⁵⁸⁰ Photolysis of the pyridazinium dicyanomethylide **285** gives a mixture of a pyrazole (**286**)



⁵⁸⁰ H. H. Perkampus and T. Bluhm, *Tetrahedron* **28**, 2099 (1972).

and a cyclopropene derivative (**287**).⁵⁸¹ In contrast to the thermolysis, photochemical decomposition of the cycloadduct **143** gave compound **146** as the main product, together with **144** and **145** and the starting pyridazinone, formed by a retro reaction.³⁴¹ The photosensitized decomposition gave the same products, except for the starting compound. Photolysis of a methanolic solution of the azidopyridazine **204** gives a mixture of compounds **205** and **288** a small amount of a pyrazole **289**.⁴⁴⁶

Reduced pyridazines have also been irradiated. The dihydropyridazine **290** gives in high yield the open-chain product **291**,⁵⁸² whereas dimethyl 1,2-dihydropyridazine-1,2-dicarboxylate gives two isomeric compounds, **292** and **293** (the minor product).⁴⁹³ It is postulated that the latter is formed by



initial N—N bond rupture and subsequent cyclization. 1,3,4-Triphenyl-1,6-dihydropyridazine is photooxidized to the -6-one, but when irradiated in the presence of fumaronitrile a [2 + 2]-cycloadduct (**294**) is formed.⁵⁶⁵ Photochemical and thermal decomposition of compound **295** was investigated to study the stereochemical course. In both cases the main product was **296** accompanied by one of the stereoisomers **297** or **298**; a high degree of retention of configuration in the products was found. The decomposition proceeds via a 1,4-biradical.⁵⁸³

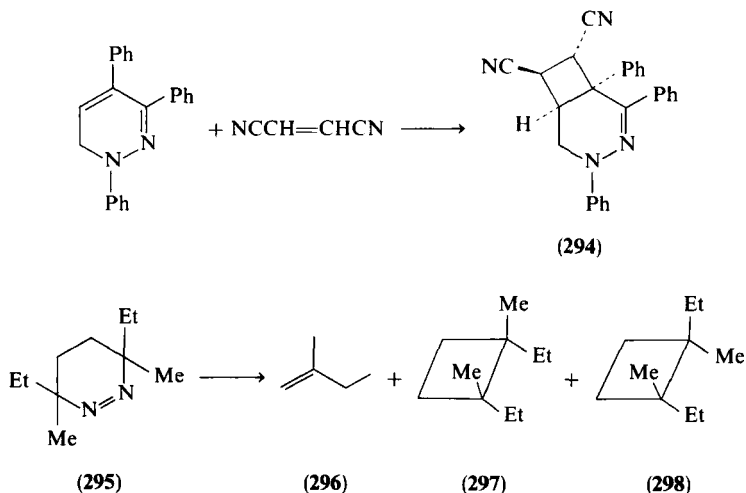
Photochemical isomerizations of perfluoropyridazines proceed in a manner different from the thermal. Here, perfluoropyrazines (**259**) are formed in high yields and their formation was postulated to involve intermediate Dewar-diazabenzenes and diazaprismane.⁵⁵⁰ Irradiation of perfluoro-4,5-diisopropylpyridazine gives the corresponding pyrazine (**301**), twice as much of a para-bonded valence-isomer (**300**).⁵⁸⁴ The mechanistic pathway was

⁵⁸¹ H. Arai, H. Igeta, and T. Tsuchiya, *Chem. Commun.*, 521 (1973).

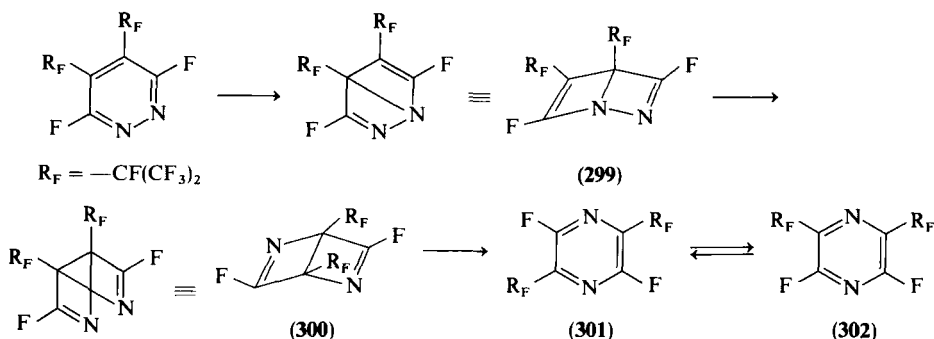
⁵⁸² J. Rigaudy and J. C. Breliere, *Bull. Soc. Chim. Fr.*, 455 (1968).

⁵⁸³ P. D. Bartlett and N. A. Porter, *J. Am. Chem. Soc.* **90**, 5317 (1968).

⁵⁸⁴ R. D. Chambers, W. K. R. Musgrave, and K. C. Srivastava, *Chem. Commun.*, 264 (1971).



further substantiated by isolation of products corresponding to **299** and **300** (Scheme 17).⁵⁸⁵ Other products are believed to result from dimerization of an intermediate azete (azacyclobutadiene) derivative.⁵⁸⁶ It was further



SCHEME 17

established that perfluoro-2,5- (**301**) and -2,6-diisopropylpyrazines (**302**) are very slowly interconverted on prolonged irradiation in the liquid phase.⁵⁸⁷ Similar pyridazine-pyrazine photorearrangement takes place also with 3,6-difluoro-4,5-dichloropyridazine giving 2,5-difluoro-3,6-dichloropyrazine.⁵⁸⁸

⁵⁸⁵ R. D. Chambers, J. R. Maslakiewicz, and K. C. Srivastava, *J.C.S. Perkin I*, 1130 (1975).

⁵⁸⁶ R. D. Chambers and J. R. Maslakiewicz, *Chem. Commun.*, 1005 (1976).

⁵⁸⁷ R. D. Chambers, J. A. H. MacBride, J. R. Maslakiewicz, and K. C. Srivastava, *J.C.S. Perkin I*, 396 (1975).

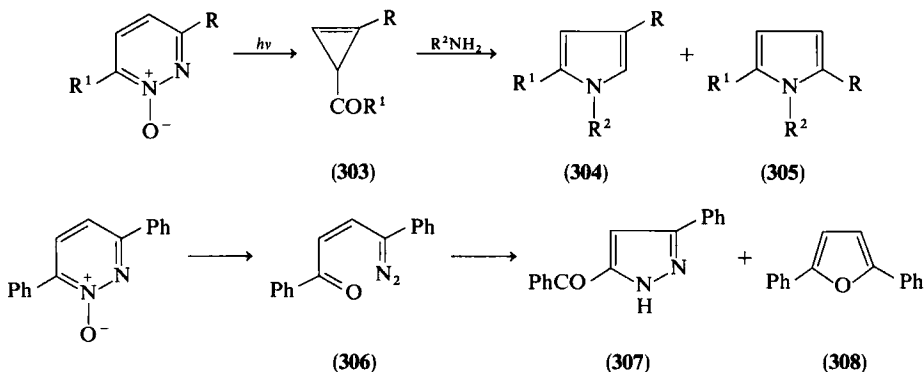
⁵⁸⁸ D. W. Johnson, V. Austel, R. S. Feld, and D. M. Lemal, *J. Am. Chem. Soc.* **92**, 7505 (1970).

Quantum yield measurements indicate that this rearrangement requires only $n \rightarrow \pi^*$ excitation.

Although the multiplicity of excited states of heteroaromatic *N*-oxides is disputed, it is established that for pyridazine *N*-oxides the triplet state is involved in oxygen abstraction reactions, whereas the singlet state is involved in rearrangements and isomerizations.⁵⁸⁹

Photoreactions of pyridazine *N*-oxides have been misinterpreted in part. Thus, the reported hydroxymethylation of some pyridazine *N*-oxides⁵⁹⁰ with concomitant loss of oxygen is probably due to secondary reaction of the parent pyridazine.⁵⁷² Igeta *et al.* reported on the photochemistry of several pyridazine *N*-oxides that resulted mainly in deoxygenation^{591–593}; in the presence of benzene, toluene, or cyclohexane, the hydrocarbons were oxygenated to give phenols or cyclohexanol in moderate yield.⁵⁹¹ Cyclohexene gave cyclohexene oxide and cyclohexanone in a ratio of 5:1; and polymethylbenzenes, the corresponding phenols or hydroxymethyl derivatives.^{592,593}

Some pyridazine *N*-oxides, when irradiated in methanol with a high-pressure mercury lamp, gave a mixture of the deoxygenated product and 4-hydroxymethylpyridazine, accompanied in some cases by 3-acylpyrazoles.⁵⁹⁰ By contrast, irradiation in the presence of primary amines gives the *N*-substituted pyrroles **304** and **305** in a ratio of about 1:2. It could be shown that isolatable cyclopropenyl ketones (**303**) are initially formed.^{594,595}



⁵⁸⁹ K. B. Tomer, N. Harrit, I. Rosenthal, O. Buchardt, P. L. Kumler, and D. Creed, *J. Am. Chem. Soc.* **95**, 7402 (1973).

⁵⁹⁰ M. Ogata and K. Kano, *Chem. Commun.*, 1176 (1967).

⁵⁹¹ H. Igeta, T. Tsuchiya, M. Yamada, and H. Arai, *Chem. Pharm. Bull.* **16**, 767 (1968).

⁵⁹² T. Tsuchiya, H. Arai, and H. Igeta, *Tetrahedron Lett.*, 2747 (1969).

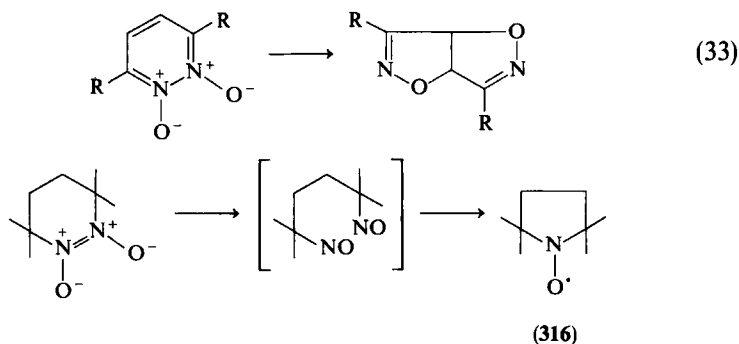
⁵⁹³ T. Tsuchiya, H. Arai, and H. Igeta, *Tetrahedron Lett.*, 2213 (1970).

⁵⁹⁴ T. Tsuchiya, H. Arai, and H. Igeta, *Chem. Commun.*, 550 (1972).

⁵⁹⁵ T. Tsuchiya, H. Arai, and H. Igeta, *Chem. Pharm. Bull.* **21**, 1516 (1973).

and isomaleimide **315**.⁶⁰⁰ A tetrahydrofuran derivative and an epoxyazo compound were identified as products of photolysis of 4,4,5,5-tetramethyl-3,6-diphenyl-4,5-dihydropyridazine 1-oxide.⁶⁰¹ If the *N*-oxide function is absent, various 1,2-diazapolyarenes are formed from tri- or tetraphenylpyridazines.⁶⁰²

Few reports on the light-induced reactions of pyridazine 1,2-dioxides have been published. Irradiation of pyridazine 1,2-dioxides, first thought to give 1,4,6,7-dioxodiazocines,⁶⁰³ affords dihydroisoxazolo[5,4-*d*]isoxazoles [Eq. (33)],⁶⁰⁴ the structure being established by X-ray analysis. It is postulated that this transformation takes place via a bisiminoxyl radical, formed by N—N bond fission, followed by ring closure. 3,3,6,6-Tetramethyl-3,4,5,6-tetrahydropyridazine 1,2-dioxide when irradiated in methanolic solution is converted in good yield into 2,2,5,5-tetramethylpyrrolidine *N*-oxyl (**316**).⁶⁰⁵ The reaction proceeds most probably via a ring-opened dinitroso species which could not be trapped.



IV. Theoretical Calculations

Several calculations on the electronic structure of pyridazine are available.^{606,607} Calculations of the polarizability⁶⁰⁸ and π -bond orders were

⁶⁰⁰ T. Tsuchiya, H. Arai, M. Hasebe, and H. Igeta, *Chem. Pharm. Bull.* **22**, 2301 (1974).

⁶⁰¹ W. M. Williams and W. R. Dolbier, *J. Am. Chem. Soc.* **94**, 3955 (1972).

⁶⁰² T. Tsuchiya, H. Arai, T. Tonami, and H. Igeta, *Chem. Pharm. Bull.* **19**, 2204 (1971).

⁶⁰³ H. Arai, A. Ohsawa, K. Saiki, and H. Igeta, *Chem. Commun.*, 133 (1977).

⁶⁰⁴ H. Arai, A. Ohsawa, K. Saiki, H. Igeta, A. Tsuji and T. Akimoto, *Chem. Commun.* 856 (1977).

⁶⁰⁵ F. D. Greene and K. E. Gilbert, *J. Org. Chem.* **40**, 1409 (1975).

⁶⁰⁶ A. Toth and E. Dudar, *Acta Chim. Acad. Sci. Hung.* **77**, 69 (1973) [*CA* **79**, 65324 (1973)].

⁶⁰⁷ T. Yonezawa, H. Kato, and H. Kato, *Theor. Chim. Acta* **13**, 125 (1969).

⁶⁰⁸ M. A. Kovner, S. K. Potapov, G. A. Rekhen, N. A. Sakhanov, and I. V. Shevchenko, *Opt. Spektrosk.* **29**, 523 (1970).

calculated and correlated with bond lengths for some pyridazines.^{609,610} Other calculations deal with total energy and binding energy of pyridazine,^{611,612} the Dewar structure of pyridazine,⁶¹³ the effect of an electric field on the absorption spectrum of pyridazine,⁶¹⁴ its transition energy,⁶¹⁵ the aromaticity index,⁶¹⁶ the dipole moment and ¹⁴N quadrupole coupling constants,⁶¹⁷⁻⁶¹⁹ and the ionization potential.⁶²⁰

The excited electronic states of pyridazine have attracted interest because of the possibility to explore the interactions of the nonbonding (*n*) orbitals of the nitrogen atoms and as a model for testing the theory of nonradiative electronic relaxation processes. Several singlet excited states of pyridazine have been examined,^{621,622} and the changes in hydrogen atom positions on electronic excitation of pyridazine were calculated.⁶²³

Calculations of pyridazine protonation were performed, and the experimental order of proton affinity as pyridine > pyridazine > pyrimidine > pyrazine were reproduced.⁶²⁴

For hetarynes principal attention has been focused on the 3,4-didehydro species although, in principle, the radical lobes can be in 3,5 or 3,6 orientations as well. The electronic structures of 3,4-, 4,5-, 3,5- and 3,6-didehydropyridazine have been calculated, and the results indicate that 4,5-didehydropyridazine is the most stable isomer when 4-halopyridazine is dehydrohalogenated.³⁵⁴

Calculations were performed also for pyridazine derivatives, such as charge densities of 3-hydrazinopyridazines,⁶²⁵ fluoro- and methoxypyridazines, and their localization energies for the nucleophilic substitution of the halogen by methoxide ion.⁶²⁶

⁶⁰⁹ G. Häfelinger, *Chem. Ber.* **103**, 3289 (1970).

⁶¹⁰ G. Häfelinger, *Tetrahedron* **27**, 1635 (1971).

⁶¹¹ M. H. Palmer, A. J. Gaskell, and R. H. Findlay, *Tetrahedron Lett.*, 4659 (1973).

⁶¹² M. H. Palmer, A. J. Gaskell, and R. H. Findlay, *J.C.S. Perkin II*, 778 (1974).

⁶¹³ Z. Latajka, H. Ratajczak, W. J. Orville-Thomas, and E. Ratajczak, *J. Mol. Struct.* **28**, 323 (1975).

⁶¹⁴ R. M. Hochstrasser, *Mol. Phys.* **24**, 597 (1972).

⁶¹⁵ M. L. Bailey, *Theor. Chim. Acta* **13**, 56 (1969).

⁶¹⁶ G. Naray-Szabo and K. Horvath, *Croat. Chem. Acta* **49**, 461 (1977).

⁶¹⁷ R. Carbo, *Ann. Quin.* **64**, 147 (1968).

⁶¹⁸ E. W. Davies and W. C. Mackrodt, *Chem. Commun.*, 1226 (1967).

⁶¹⁹ N. S. Hush and J. R. Yandle, *Chem. Phys. Lett.* **1**, 493 (1967).

⁶²⁰ J. Del Bene and H. H. Jaffé, *J. Chem. Phys.* **50**, 563 (1969).

⁶²¹ T. M. Bustard and H. H. Jaffé, *J. Chem. Phys.* **53**, 534 (1970).

⁶²² B. F. Samsonov, A. F. Terpugova, and E. I. Cheglov, *Teor. Eksp. Khim.* **13**, 106 (1977).

⁶²³ K. K. Innes and R. M. Lucas, *J. Mol. Spectrosc.* **24**, 247 (1967).

⁶²⁴ J. E. Del Bene, *J. Am. Chem. Soc.* **99**, 3617 (1977).

⁶²⁵ V. M. Kulkarni, *Indian J. Biochem. Biophys.* **12**, 367 (1975).

⁶²⁶ H. F. Beer and D. T. Clark, *J. Fluorine Chem.* **4**, 181 (1974).

Calculations have been applied to the problem of tautomerism of maleic hydrazide⁶²⁷ and other pyridazinones.^{628,629} The lactam structure was found to be the most stable, but in the case of 3-amino-4-hydroxypyridazine the aminol form is energetically most favorable.⁶²⁹

V. Physical and Spectral Properties

Ionization constants of hydroxy- and mercaptopyridazines,^{630,631} of amino- and diaminopyridazines and their quaternization products,²⁷⁴ of methylsulfinylpyridazines,⁴⁴⁰ and of pyridazinium ylides have been recorded.^{632,633} The basicities of a series of pyridazines have been determined and correlated with substituent constants using the Hammett free-energy relationship.⁶³⁴ The magnetic susceptibility of pyridazine was measured,⁶³⁵ and the rate constant for the reaction of hydrogen atoms with pyridazine was determined.⁶³⁶ The experimental dipole moment, Kerr constant, and molar Cotton-Mouton constant, obtained at 298°K and 633 nm, are reported.⁶³⁷ The magnetic circular dichroism spectrum of pyridazine has been measured.⁶³⁸

Studies on the tautomerism of pyridazines with potential tautomeric groups have continued. On the basis of recorded ionization constants and UV spectra of 3,4,5-trimercaptopyridazine and its derivatives, it is concluded that the compound exists as 3,4-dimercaptopyridazine-5(2*H*)-thione.⁶³⁹ Tautomerism of hydroxy- and mercaptopyridazines was investigated with the aid of the corresponding anhydro bases as reference compounds.⁶⁴⁰ They exist predominantly in the -one or -thione forms. Similarly, the 3-mercaptopyridazine-6(1*H*)-thione structure in aqueous solution has been redeter-

⁶²⁷ M. Augustin, H. D. Schädler, and P. Reinemann, *Z. Chem.* **12**, 230 (1972).

⁶²⁸ G. La Manna and M. Cignitti, *Gazz. Chim. Ital.* **102**, 325 (1972).

⁶²⁹ G. Rasch, *Wiss. Z. Tech. Hochsch. Chem. "Carl Schorlemmer" Leuna-Merseburg* **10**, 297 (1968).

⁶³⁰ G. B. Barlin, *J.C.S. Perkin II*, 1199 (1974).

⁶³¹ I. V. Turovskii, V. T. Glezer, L. Ya. Avota, Ya. Stradins, and S. Giller, *Khim. Geterotsikl. Soedin.*, 993 (1973).

⁶³² M. Petrovanu, E. Stefanescu, and I. Druta, *Rev. Roum. Chim.* **16**, 1107 (1971).

⁶³³ W. G. Phillips and K. W. Ratts, *J. Org. Chem.* **35**, 3144 (1970).

⁶³⁴ R. F. Cookson and G. W. H. Cheeseman, *J.C.S. Perkin II*, 392 (1972).

⁶³⁵ J. D. Wilson, *J. Chem. Phys.* **53**, 467 (1970).

⁶³⁶ P. Neta and R. H. Schuler, *J. Am. Chem. Soc.* **94**, 1056 (1972).

⁶³⁷ M. R. Battaglia and G. L. D. Ritchie, *J.C.S. Perkin II*, 879 (1977).

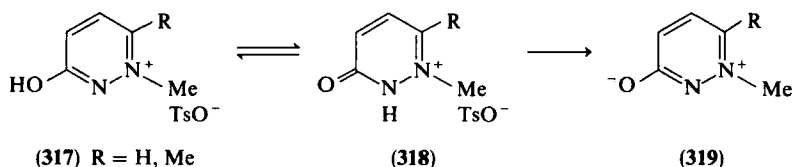
⁶³⁸ A. Kaito, M. Hatano, and A. Tajiri, *J. Am. Chem. Soc.* **99**, 5241 (1977).

⁶³⁹ G. B. Barlin and P. Lakshminarayana, *J.C.S. Perkin I*, 1038 (1977).

⁶⁴⁰ G. B. Barlin and A. C. Young, *J. Chem. Soc. B*, 1261 (1971).

mined.⁶³⁰ The structures of 1-substituted maleic hydrazides were studied by infrared spectroscopy. Although the monohydroxy form is usually preferred,^{80,81} it is suggested that 2-nitrophenyl- and 2,4-dinitrophenyl-substituted maleic hydrazides exist in the dioxo form.^{82,83}

The synthesis of betaines of several aromatic azines and their benzologs by Katritzky *et al.* stimulated also investigations of the corresponding pyridazines.⁶⁴¹ They were prepared by methylation of the corresponding pyridazinones with methyl toluene-*p*-sulfonate to **317** and subsequent conversion into betains (**319**). Contrary to other related betaines, compounds of the type **319** are unreactive toward a variety of dipolarophiles. The hydroxy form of the cation (**317**) was shown to predominate over the oxo form (**318**).⁶⁴¹ UV, IR, and NMR data have been used for structure examination of betaines (**95**)²²⁰ and some pyridazinones.⁶⁴² NMR spectra established



the predominance of the 3-hydroxy form for 3-hydroxypyridazine 1-oxide and its monomethyl derivatives.⁶⁴³

UV spectra of pyridazines and pyridazinones were recorded, and solvent effects on spectra were examined.^{644–652} The absorption spectrum of the pyridazine radical was reported.⁶⁵³ Resonance fluorescence has been observed from pyridazine vapor.⁶⁵⁴ Electron transmission spectroscopy has

⁶⁴¹ N. Dennis, A. R. Katritzky, and M. Ramaiah, *J.C.S. Perkin I*, 1506 (1975).

⁶⁴² E. Yu. Gudriniece and A. H. Karklins, *Latv. PSR Zinat. Akad. Vestis, Kim. Ser.*, 474 (1967) [*CA* **68**, 105136 (1968)].

⁶⁴³ H. Igeta, T. Tsuchiya, M. Nakajima, and H. Yokogawa, *Chem. Pharm. Bull.* **17**, 763 (1969).

⁶⁴⁴ G. Launay and B. Wojtkowiak, *Bull. Soc. Chim. Fr.*, 3036 (1969).

⁶⁴⁵ G. Launay and B. Wojtkowiak, *C.R. Acad. Sci., Ser. C* **276**, 225 (1973).

⁶⁴⁶ T. G. Meister, G. Ya. Zelikina, L. V. Golovina, and V. V. Fesik, *Opt. Spektrosk.* **37**, 903 (1974).

⁶⁴⁷ K. K. Innes, W. C. Tincher, and E. F. Pearson, *J. Mol. Spectrosc.* **36**, 114 (1970).

⁶⁴⁸ B. K. Das, *J. Indian Chem. Soc.* **45**, 1075 (1968).

⁶⁴⁹ A. A. Nada, M. S. A. Abd El-Mottaleb, and A. M. Mourad, *J. Prakt. Chem.* **319**, 369 (1977).

⁶⁵⁰ D. C. Iffland, M. P. McAneny, and D. J. Weber, *J. Chem. Soc. C*, 1703 (1969).

⁶⁵¹ K. N. Zelenin, L. M. Korzhikova, and O. V. Sverdlova, *Zh. Prikl. Spektrosk.* **11**, 1080 (1969).

⁶⁵² F. G. Baddar, N. F. Eweiss, M. Nosseir, and N. Latif, *Spectrochim. Acta, Part A* **34**, 837 (1976).

⁶⁵³ A. Grimison, G. A. Simpson, and M. Trujillo Sanchez, *Quantum Aspects Heterocycl. Compds. Chem. Biochem., Proc. Int. Symp.*, 2nd p. 250 (1969) [*CA* **75**, 145747 (1971)].

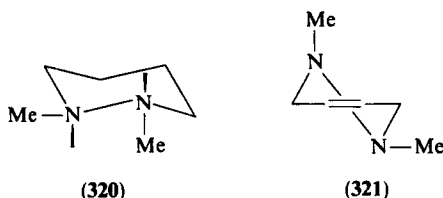
⁶⁵⁴ A. D. Jordan and C. S. Parmenter, *Chem. Phys. Lett.* **16**, 437 (1972).

been used to study in pyridazine the configuration of the ground state plus an electron in one of the lowest empty orbitals (π^*). A correlation has been made between the gas-phase electron affinity and the polarographic potential.^{655,656}

IR spectra of pyridazines and polypyridazines were studied with respect to interactions with the side chain.⁶⁵⁷ The IR spectral shift due to hydrogen-bonding between methanol and pyridazine (and other azines) was determined; the $\Delta\nu$ was compared with the pK_a .⁶⁵⁸ In connection with the structure of maleic hydrazide and its methyl derivatives, the Raman spectrum of the 1,2-dimethyl derivative was recorded and helped to explain the anomalously low reported IR carbonyl frequency.⁶⁵⁹ The laser Raman polarization spectrum of the lattice vibrational region of pyridazine was reported.⁶⁶⁰

NMR spectroscopy has been widely used in particular to study the conformations and conformational interconversions of reduced pyridazines. The conformations of tetra- and hexahydropyridazines have been extensively studied by several groups in order to examine the influence of steric and electronic effects upon the geometry of the hydrazine part of the molecule. The temperature dependence of their NMR spectra was used to examine ring inversion and nitrogen inversion processes.

For 1,2-dimethylhexahydropyridazine, on the basis of temperature-dependent NMR spectrum, the prevailing conformation **320** was proposed and a barrier of ca. 12 kcal mol⁻¹ was calculated.⁶⁶¹ These conformational



changes were reinterpreted,⁶⁶² and the above barrier was ascribed to the nitrogen inversions or ring inversions which involve a crossing of the two *N*-methyl groups. The earlier conclusion that this compound exists almost

⁶⁵⁵ I. Nenner and G. J. Schulz, *J. Chem. Phys.* **62**, 1747 (1975).

⁶⁵⁶ M. N. Pisanias, L. G. Christophorou, J. G. Carter, and D. L. McCorkle, *J. Chem. Phys.* **58**, 2110 (1973).

⁶⁵⁷ I. Gabe, E. Mantaluta, and G. Neamtu, *Rev. Roum. Chim.* **14**, 1163 (1969).

⁶⁵⁸ L. Joris and P. Rague Schleyer, *Tetrahedron* **24**, 5991 (1968).

⁶⁵⁹ J. M. Chalmers, M. E. A. Cudby, D. Smith, and P. J. Taylor, *Spectrochim. Acta, Part A* **31**, 1547 (1975).

⁶⁶⁰ R. H. Larkin and H. D. Stidham, *Spectrochim. Acta, Part A* **29**, 781 (1973).

⁶⁶¹ J. E. Anderson, *J. Am. Chem. Soc.* **91**, 6374 (1969).

⁶⁶² R. A. Y. Jones, A. R. Katritzky, and R. Scattergood, *Chem. Commun.*, 644 (1971).

completely in the diequatorial conformer⁶⁶¹ was revised, so that three conformations, i.e., with methyl groups aa, ee, or ea, are populated.^{663,664} Similar results were found with other derivatives.⁶⁶⁴ Although a ratio of aa, ee, and ea conformers of 62:20:18 at room temperature,⁶⁶⁵ was consistent with the dipole moment data, ¹³C NMR studies allowed more accurate estimates of conformational populations and showed unambiguously that for 1,2-dimethylhexahydropyridazine the diequatorial form predominates slightly in solution and the diaxial conformer is not present in detectable concentration at low temperatures.⁶⁶⁶⁻⁶⁶⁸ Introduction of additional methyl groups at the carbons α to the ring nitrogens changes the conformation, and the ea is then the predominant conformer, as shown by photoelectron^{669,670} and ¹³C-NMR spectra.^{667,668} For 1,2-diphenylhexahydropyridazine, however, from photoelectron spectra it is concluded that the phenyl groups are aa oriented.⁶⁷¹ To study the geometry of hexahydropyridazines, ESR spectra were also recorded and interpreted,⁶⁷² and cyclic voltametry was applied.⁶⁷³⁻⁶⁷⁵ From ESR studies on some substituted hexahydropyridazinium radical cations it is concluded that these have a planar or nearly planar geometry of the hydrazinium part of the molecule.⁶⁷⁶

1,2-Disubstituted tetrahydropyridazines have been of particular interest for studies of stereomutation at ring nitrogens. The results show that in these molecules at least two distinct conformational equilibria can take place.⁸ However, there was some controversy in the assignment of the specific processes, i.e., ring inversion, ring-nitrogen inversion, and restricted rotation about the N—R bonds. Variable temperature NMR measurements of 1,2-dicarbethoxy-1,2,3,6-tetrahydropyridazine and its dicarbotrifluoroethoxy analog indicate that they exist in at least four distinct conformational

⁶⁶³ R. A. Y. Jones, A. R. Katritzky, D. L. Ostercamp, K. A. F. Record, and A. C. Richards, *Chem. Commun.*, 644 (1971).

⁶⁶⁴ R. A. Jones, A. R. Katritzky, D. L. Ostercamp, K. A. F. Record, and A. C. Richards, *J.C.S. Perkin II*, 34 (1972).

⁶⁶⁵ R. A. Y. Jones, A. R. Katritzky, K. A. F. Record, and R. Scattergood, *J.C.S. Perkin II*, 406 (1974).

⁶⁶⁶ S. F. Nelsen and G. R. Weisman, *J. Am. Chem. Soc.* **96**, 7111 (1974).

⁶⁶⁷ S. F. Nelsen and G. R. Weisman, *J. Am. Chem. Soc.* **98**, 3281 (1976).

⁶⁶⁸ G. R. Weisman and S. F. Nelsen, *J. Am. Chem. Soc.* **98**, 7007 (1976).

⁶⁶⁹ S. F. Nelsen, J. M. Buschek, and P. J. Hintz, *J. Am. Chem. Soc.* **95**, 2013 (1973).

⁶⁷⁰ S. F. Nelsen and J. M. Buschek, *J. Am. Chem. Soc.* **96**, 6987 (1974).

⁶⁷¹ P. Rademacher, V. M. Bass, M. Wildemann, and H. Weger, *Chem. Ber.* **110**, 1939 (1977).

⁶⁷² S. F. Nelsen and P. J. Hintz, *J. Am. Chem. Soc.* **93**, 7105 (1971).

⁶⁷³ S. F. Nelsen and P. J. Hintz, *J. Am. Chem. Soc.* **94**, 7108 (1972).

⁶⁷⁴ S. F. Nelsen, L. Echegoyen, and D. H. Evans, *J. Am. Chem. Soc.* **97**, 3530 (1975).

⁶⁷⁵ S. F. Nelsen, L. Echegoyen, E. L. Clennan, D. H. Evans, and D. A. Corrigan, *J. Am. Chem. Soc.* **99**, 1130 (1977).

⁶⁷⁶ F. A. Neugebauer and H. Weger, *Tetrahedron Lett.*, 2083 (1976).

isomers.⁶⁷⁷ Anderson proposed that in 1,2-dimethyl-1,2,3,6-tetrahydropyridazine, where steric strain in the ring plays a smaller role, the preferred conformation is **321**.⁶⁶¹ Barriers to nitrogen inversion of this and related compounds are as high as 11.7–13.3 kcal mol⁻¹. The barriers to ring inversion for tetrahydropyridazine are 8.2–9.5 kcal mol⁻¹ and this enhancement, when compared to cyclohexene (5.4 kcal mol⁻¹) is postulated to originate from the intrinsically greater barrier to rotation about N—N and N—C bonds than about C—C bonds.⁶⁶¹ Also photoelectron spectra of tetrahydropyridazines support the conformation **321** with pseudoequatorial and pseudoaxial *N*-methyl groups.⁶⁷⁰ Investigations of related substituted tetrahydropyridazines^{678,679} in general showed similar orientation to hexahydropyridazines, the *N*-methyl groups being one equatorial and one axial. It was further concluded that the barrier to ring inversion is smaller than the barrier to nitrogen inversion.

¹H NMR spectra of many pyridazines were recorded. NMR studies of oriented pyridazine^{680,681} and solvent shifts of pyridazine and 3-methylpyridazine have been reported, and the additivity of solvent shifts was established.⁶⁸² NMR spectra of pyridazinones were measured to investigate the influence of substituents on chemical shifts.^{683,684} Chemical shifts and coupling constants were used to determine the configuration of anomeric 2-deoxyribofuranosylpyridazinones,^{685,686} and NMR, UV, and CD spectroscopic studies on glucopyranosides and 2-deoxyribofuranosides of pyridazines have been reported.^{687,688}

The wideline NMR, IR, and Raman spectra of maleic hydrazide were determined and discussed in connection with its tautomeric forms.⁶⁸⁹ NMR techniques have been used to predict the structure of cyclization products from 3-carboxyacryloylhydrazines.⁷⁵ The NMR spectra of *N*-methylpyridazinium iodides and pyridazine *N*-oxide were investigated, and the

⁶⁷⁷ E. W. Bittner and J. T. Gerig, *J. Am. Chem. Soc.* **94**, 913 (1972).

⁶⁷⁸ J. Firl, *Chem. Ber.* **102**, 2177 (1969).

⁶⁷⁹ P. Ogden, *Chem. Commun.*, 1084 (1969).

⁶⁸⁰ E. E. Burnell and C. A. DeLange, *Mol. Phys.* **16**, 95 (1969).

⁶⁸¹ C. L. Khetrapal, A. C. Kunwar, and A. V. Patankar, *Liq. Cryst., Proc. Int. Conf.* p. 471 (1973) [*CA* **84**, 144760 (1976)].

⁶⁸² P. Laszlo and J. L. Soong, *J. Chem. Phys.* **47**, 4472 (1967).

⁶⁸³ Y. Maki, M. Suzuki, T. Masugi, and M. Takaya, *Gifu Yakka Daigaku Kiyo* **16**, 41 (1966) [*CA* **68**, 48849 (1968)].

⁶⁸⁴ G. Scapini, F. Duro, and R. Mondelli, *Chim. Ind. (Milan)* **50**, 1328 (1968).

⁶⁸⁵ P. Nuhn, A. Zschunke, D. Heller, and G. Wagner, *Tetrahedron* **25**, 2139 (1969).

⁶⁸⁶ A. Zschunke, P. Nuhn, D. Heller, and G. Wagner, *Z. Chem.* **11**, 68 (1971).

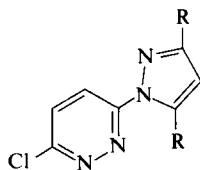
⁶⁸⁷ P. Nuhn, A. Zschunke, and G. Wagner, *Z. Chem.* **9**, 335 (1969).

⁶⁸⁸ P. Nuhn, D. Heller, G. Wagner, and A. Zschunke, *J. Prakt. Chem.* **313**, 614 (1971).

⁶⁸⁹ B. Lippert, H. P. Fritz, and P. Burkert, *Chem. Ber.* **108**, 478 (1975).

calculated coupling constants were correlated with the observed ones.⁶⁹⁰ The results are claimed to be more satisfactory than those obtained earlier by Gil and Pinto.⁶⁹¹

The free energies of activation for rotation about the =CHNMe_2 bond in some pyridazinyl-substituted dimethylformamidines have been determined,⁶⁹² and research on *N*-(3-pyridazinyl)formamidoxime has provided evidence that the compound exists in the oxime, not in the hydroxylamino, form.⁶⁹³ From NMR data it is concluded that pyridazinylpyrazoles have the *trans*-coplanar conformation **322**.⁶⁹⁴ The NMR spectrum of ^{15}N -



(322) R = H, Me

pyridazine was determined, and coupling constants were calculated⁶⁹⁵; these were also reinvestigated for pyridazine.^{691,696,697} $\text{Eu}(\text{DPM})_3$ -induced shifts of the proton resonances of pyridazine were determined, and a rapid interconversion between equivalent complexes is assumed.⁶⁹⁸

^{13}C -NMR data of pyridazines and *N*-oxides⁴³⁴ and of maleic hydrazide are reported.⁶⁹⁹ The ^{13}C chemical shifts of pyridazine and its cation were calculated,⁷⁰⁰ measured as function of pH in aqueous solution,⁷⁰¹ and later improved.^{702,703}

The ^{14}N -NMR chemical shifts of pyridazine and other azines depend almost linearly on the π -charge density at the nitrogen atom.⁷⁰⁴ The ^{14}N

⁶⁹⁰ D. J. Elias, A. G. Moritz, and D. B. Paul, *Aust. J. Chem.* **25**, 427 (1972).

⁶⁹¹ V. M. S. Gil and A. J. L. Pinto, *Mol. Phys.* **19**, 573 (1970).

⁶⁹² M. Zupan, V. Pirc, A. Pollak, B. Stanovnik, and M. Tišler, *J. Heterocycl. Chem.* **11**, 525 (1974).

⁶⁹³ S. Polanc, B. Verček, B. Stanovnik, and M. Tišler, *J. Heterocycl. Chem.* **11**, 103 (1974).

⁶⁹⁴ J. Elguero, R. Jacquier, and S. Mondon, *Bull. Soc. Chim. Fr.*, 1346 (1970).

⁶⁹⁵ J. P. Jacobsen, O. Snerling, E. J. Pedersen, J. T. Nielsen, and K. Schaumburg, *J. Magn. Reson.* **10**, 130 (1973).

⁶⁹⁶ V. M. S. Gil and A. J. L. Pinto, *Mol. Phys.* **16**, 623 (1969).

⁶⁹⁷ V. M. S. Gil and A. J. L. Pinto, *Rev. Port. Quim.* **11**, 219 (1969).

⁶⁹⁸ W. L. F. Armarego, T. J. Batterham, and J. R. Kershaw, *Org. Magn. Reson.* **3**, 575 (1971).

⁶⁹⁹ H. P. Fritz, F. Köhler, and B. Lippert, *Chem. Ber.* **106**, 2918 (1973).

⁷⁰⁰ W. Adam, A. Grimison, and G. Rodriguez, *J. Chem. Phys.* **50**, 645 (1969).

⁷⁰¹ E. Breitmaier and K. H. Spohn, *Tetrahedron* **29**, 1145 (1973).

⁷⁰² G. Pouzard and M. Rajzmann, *Org. Magn. Reson.* **8**, 271 (1976).

⁷⁰³ T. Tokuhiko and G. Fraenkel, *J. Am. Chem. Soc.* **91**, 5005 (1969).

⁷⁰⁴ M. Witanowski, L. Stefaniak, H. Januszewski, and G. A. Webb, *Tetrahedron* **27**, 3129 (1971).

pure quadrupole resonance spectrum of pyridazine was measured.⁷⁰⁵ Chemical shift ¹⁹F-NMR data for ring fluorine atoms in perfluoroalkyl-pyridazines have been useful for structure assignments.⁴¹¹ ³⁵Cl-NMR spectra of chloropyridazines and chloropyridazinones were recorded.⁷⁰⁶⁻⁷⁰⁸

The photoelectron spectrum of pyridazine is similar to those of pyrazine, pyrimidine, and triazine; i.e., the lowest ionization potential corresponds to ionization of a lone-pair electron.^{709,710} The ionization potential is in agreement with the calculated value.⁷¹¹ These spectra were recorded also of pyridazine 1-oxide and 1,2-dioxide, and it was found that the perturbation of the π -system by the N—O group results in the separation of the lower excited states of the *N*-oxide ions.⁷¹²

The photoelectron spectra of some 3,4,5,6-tetrahydropyridazines, their *N*-oxides and 1,2-dioxides were measured, and the energy of the highest occupied π -orbital increases in the above order in these compounds.^{713,714} From photoelectron spectra the conformations of hexahydropyridazine, its 1,2-dimethyl derivative, and 1,2-dimethyl-1,2,3,6-tetrahydropyridazine were analyzed. The dihedral angles between the electron lone-pairs are found to be 65°–67°, but in the prevailing conformer of 1,2-dimethylhexahydropyridazine the angle is about 170°. This corresponds to *c,c* methyl groups.^{669,715,716} For hexahydropyridazine, being in a *gauche* conformation, the angle was found to be 95°.⁷¹⁷ Photoelectron spectra of fluoro-substituted pyridazines were also recorded; replacement of hydrogen atoms by fluorine greatly facilitates the analysis.⁷¹⁸

The mass spectral fragmentation of many pyridazines was investigated.^{719–724} Studies of fragmentation of 2,3,4,5-tetrahydropyridazin-3-ones revealed that four principal fragmentation paths can be observed: i.e., loss

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of CO or a substituted radical, and formation of a nitrile or isocyanate ion.⁷²⁵ The ion kinetic energy (IKE) spectrum of pyridazine was studied.^{726,727}

Finally, it should be mentioned that several analytical methods for chromatographic separation and identification of pyridazines have been developed.⁷²⁸⁻⁷³⁴ Also polarographic determination⁷³⁵ and other analytical methods were applied.^{736,737} Pyridazines have been proposed as analytical reagents for the spectrophotometric determination of iron^{738,739} or for the qualitative determination of sodium.⁷⁴⁰

VI. Crystal Structures and Molecular Complexes

The crystal and molecular structures of several pyridazines were determined by Ottersen.⁷⁴¹⁻⁷⁴⁶ Significant differences occur for pyridazinones: 4,5-dichloro-3,6-pyridazinedione and 1-methyl-3,6-pyridazinedione crystallize in the monolactim form.^{741,743} The monohydroxy form was confirmed

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also for maleic hydrazide.⁷⁴⁷ From the molecular structure of protonated pyridazine, there is no indication that the protonation affects the bond lengths.⁷⁴⁵ The orientation and structure of pyridazine in a lyotropic liquid crystal was investigated,⁷⁴⁸ and the crystal structure of *N,N*-dimethyl-*N'*-(6-chloro-3-pyridazinyl)formamidine has been reported.⁷⁴⁹ Bond lengths and angles were calculated for pyridazine and its 3,6-dichloro analog from electron diffraction and microwave data.⁷⁵⁰

Pyridazine forms a stable adduct with iodine,^{751–755} with semiconductor properties.^{756–758} Similar complexes were prepared from iodine monochloride, bromine,⁷⁵³ and nickel(II) ethyl xanthate.⁷⁵⁹ Complexes of pyridazines with iron carbonyls and with iron carbonyls and triphenylphosphine have been prepared and investigated.^{760–766} Complexes of pyridazines with boron trihalides,⁷⁶⁷ silver salts,⁷⁶⁸ mercury(I) salts,^{769,770} iridium salts,^{771–774} ruthenium salts,^{775,776} and chromium carbonyls are re-

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ported.⁷⁷⁷ A number of transition metal complexes with pyridazines have been prepared,^{770,778-782} and their magnetic susceptibilities were studied.^{783,784} The crystal structure of a CuCN complex⁷⁸⁵ and one with bismuth were determined.⁷⁸⁶ The ¹H broadline NMR spectrum of bis(salicylaldehyde)pyridazine-Co(II) complex was examined at various temperatures.⁷⁸⁷ Some hydrazones of 3-acetylpyridazine were prepared for possible use as metal-chelating agents.⁷⁸⁸

VII. Biological Activity and Other Uses

Many pyridazines have biological activity or have been tested for their pharmacological activity. Pyridazine derivatives have been shown to possess hypotensive activity,^{17,789-801} antibacterial and antifungal

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activity,^{436,802-808} anti-inflammatory and analgesic activity,^{541,809-816} antiviral,^{803,817,818} antimalarial,⁸¹⁹ and antitumor activity,⁸²⁰ and to show anticancer,⁸²¹ bronchodilator,⁸²² ganglioplegic,⁸²³ and antitrichomonal effects.⁸²⁴ Furthermore, pyridazine derivatives have psychotropic activity,⁸²⁵ they depress spinal motor activity,⁸²⁶ they have sensitizing qualities,⁸²⁷ they act by limiting the transport of choline across the nerve membrane,⁸²⁸ they decrease cyclic-AMP phosphodiesterase activity,⁸²⁹

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blood levels of pyruvate and lactate⁸³⁰ and plasma total protein sodium and potassium levels,⁸³¹ and they inhibit lactate dehydrogenase activity.^{832,833}

Many pyridazine derivatives were tested for analgesic activity,^{162,487,834-840} for antimicrobial,⁸⁴¹⁻⁸⁴⁵ tuberculostatic,^{846,847} and hypoglycemic activity as antidiabetics,^{848,849} for activity on the central nervous system,⁸⁵⁰ for anticoccidial,⁸⁵¹ insecticidal,⁸⁵² and fungicidal activity,⁸⁵³ for inhibition of mitochondrial monoamine oxidase,⁸⁵⁴ for their action on the metabolism of rat cerebral cortex slices,^{855,856} and against the enzyme

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ribonucleotide diphosphate reductase of human tumor origin.⁸⁵⁷ For solubilization purposes *N*-*n*-propylaminoacetyl derivatives of pyridazine sulfonamides were prepared.⁸⁵⁸ The effect of 4,5-dibromopyridazin-6-ones on various enzymes was investigated.^{859,860}

Pyridazine derivatives influence plant growth⁸⁶¹⁻⁸⁶⁴ and are effective in weed control.⁸⁶⁵⁻⁸⁶⁸ Herbicidal activity of aryloxy pyridazines⁸⁶⁹⁻⁸⁷² and other pyridazines was investigated.⁸⁷³⁻⁸⁷⁵ Maleic hydrazide has been used extensively as a sucker-inhibiting agent in tobacco fields in the United States.^{876,877}

Pyridazine herbicides reduce or inhibit photosynthesis⁸⁷⁸⁻⁸⁸⁰ and carotenoid biosynthesis,⁸⁸¹⁻⁸⁸⁷ and they interfere with the formation of polar

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lipids of chloroplast membranes.⁸⁸⁸ Further, it was shown that they disrupt chloroplast morphology and development,⁸⁸⁹⁻⁸⁹¹ inhibit photosynthetic phosphorylation,^{892,893} and also influence the nitrogen metabolism in sugar beet.⁸⁹⁴ Investigated also was the absorption of some pyridazine herbicides in plants⁸⁹⁵⁻⁸⁹⁸ and in soil,⁸⁹⁹ the effect of pyridazines on phosphorus metabolism in plants,⁹⁰⁰ the metabolism of some phenoxypyridazines and pyridazinones in plants^{901,902} and their photodecomposition.⁹⁰³ Soil degradation of herbicidal pyridazinones was investigated⁹⁰⁴ and the bacterial degradation products of 5-amino-4-chloro-2-phenylpyridazin-3-one were identified.⁹⁰⁵ Thio- and dithio-phosphoric acid esters of pyridazinones were prepared and tested for pesticidal activity.⁹⁰⁶⁻⁹⁰⁹

Merocyanine dyes have been prepared from pyridazinones,⁹¹⁰ and many pyridazines with an unsaturated side chain were synthesized in order to

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